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Treatment and Prognosis in The Leukemias and Allied Disorders

CYRUS C. STURGIS*

UNIVERSITY OF MICHIGAN MEDICAL SCHOOL, ANN ARBOR

Currently, we have no cures for patients with leukemia and allied disorders. However, there are available a number of agents which, judiciously employed, alone or in combination, may contribute significantly to the health and life of such patients. On the basis of his own clinical experience, the author assesses various chemotherapeutic agents as well as different types of x-ray therapy, and discusses their applicability to specific disease states.

Leukemia is now generally regarded as a neoplastic disorder arising primarily in the blood-forming organs. The leukemic cells have the characteristics of cancer cells as they exhibit definite evidences of unrestrained growth. The etiology of the condition is as obscure as is the cause of any neoplasm. There are, however, several known factors which may have a bearing on its etiology.

In the first place, there has been an increase of several times in the incidence since 1920. This is not because more people live to the age when they acquire leukemia, as the increase is present in the groups from infancy to old age. It is in part due to the fact that the disease is now recognized in more instances because of improved diagnostic methods; especially is this true of the subleukemic types. This does not account for the entire increase, however, in the opinion of those who have made a study of this phase of the disease. It is now estimated that leukemia is responsible for more than 5000 deaths annually in the United States, which is a larger number than is attributed to either the anemias, whooping cough, dysenteries or alcoholism.

Recent studies have established that there is a definite hereditary trend in leukemia. For some years it has been known that the disease may be transmitted in mice to as many as 90 per cent of the offspring of certain strains developed by inbreeding. The observations of Videbaek[1] have emphasized the significant role played by heredity in the etiology of leukemia and indicate that the disorder is probably related to cancer genetically. In studying 209 patients with over 4000 relatives, he found the incidence of leukemia was about 16 times as great among the relatives as in a control group of comparable ages and sex distribution. This investigator also pointed out that the cancer risk in the relatives of patients with leukemia was about 31 per cent, whereas in the population at large it was considered to be about 20 per cent. He concluded that leukemia is associated with a chromosomal inheritance which is not transmitted as such, but as an inherited disposition to the disorder.

Another fact which may be of etiologic significance is the increased incidence of the disorder in radiologists who are repeatedly exposed to roentgen rays. Studies show that leukemia occurs in radiologists about eight times[2] more frequently than in physicians not exposed to roentgen rays. For the present it seems logical to conclude that leukemia develops in any given patient as a result of an inherited disposition to the disorder, but certain unidentified environmental factors are necessary to precipitate the disease in any given case. The only known such cause at present is the exposure to small doses of roentgen rays day after day for long periods.

PATHOLOGY OF LEUKEMIA

There are four important pathologic changes which may occur in this disease. They may be summarized as follows:

1. The *anemia* which is almost always due to an infiltration of the bone marrow with an encroachment of the leukemic cells on the red

*From the Thomas Henry Simpson Memorial Institute for Medical Research, University of Michigan, Ann Arbor, Michigan.

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CYRUS C. STURGIS

blood cell-forming marrow tissues. In other words, the anemia is a myelophthisic type in most instances. Occasionally a patient may, for some unknown reason, develop a hemolytic anemia due to overactivity of the spleen.

2. *Lack of resistance toward infection,* which is due largely to the inability of the white blood cells, both mature and immature, to protect the body against infection by phagocytosis. Furthermore, apparently patients with leukemia are unable to develop antibodies normally, possibly as the result of some unknown alteration in the hematopoietic system.

3. *Impairment of the function of many tissues of the body due largely to the leukemic infiltration;* this process is an invasive one, and resembles, to a certain extent, a true neoplasm.

4. *A secondary thrombopenic purpura* with a diminution or absence of platelets from the circulating blood develops in all patients eventually. This is associated with an abnormal tendency to bleed and at necropsy patients with leukemia show extensive hemorrhages throughout all of their tissues. The cause of the thrombopenia is a diminution in the number of megakaryocytes—the precursors of the blood platelets in the bone marrow—due to their elimination by the leukemia infiltration.

TREATMENT

There are now eight types of therapy which may be employed in treatment of leukemia. They are as follows:

1. Blood transfusions.
2. Antibiotics.
3. Roentgen ray therapy.
4. Radioactive phosphorus.
5. Urethane.
6. Nitrogen mustard.
7. Folic acid antagonists.
8. ACTH and cortisone.

Blood transfusions—All patients eventually develop a normocytic, normochromic anemia, which appears in the chronic type slowly and in the acute type with much greater rapidity. There is no effective specific form of therapy for this anemia, that is, it is not benefited by iron, folic acid, liver extract, vitamin B_{12}, or other anti-anemia preparations. Temporary improvement may follow any form of therapy which controls the leukemia, such as roentgen ray and other effective measures.

The most satisfactory way to combat the anemia, however, in addition to the specific forms of therapy directed against the leukemia, is by repeated blood transfusions. In my opinion, any patient with leukemia should receive blood transfusions of 500 cc. each, daily or every other day, until the hemoglobin is raised to a level of 12 gm. (77 per cent) or higher. Furthermore, it should be maintained at this level by additional blood transfusions as indicated. Blood transfusions benefit the patient only in that they contribute hemoglobin to the circulating blood. It has not been my experience that it is possible to increase the number of white blood cells or the platelet count by this form of treatment.

Treatment of infection—All patients with leukemia, especially of the acute and subacute types, have a lowered resistance to infection. This is often a prominent feature of the clinical picture for which therapy must be directed. With the lack of resistance of the body, the bacteria which are normally present on the mucous membranes of the mouth and nose, rectum and vagina may invade the tissues and cause ulcerative lesions, and sometimes gangrenous areas. The most effective treatment of such infections is with antibiotics in the form of penicillin in doses of 1,200,000 to 3,000,000 units or more in 24 hours. If the organism is resistant to one type of antibiotic preparation, then others such as aureomycin or terramycin should be tried.

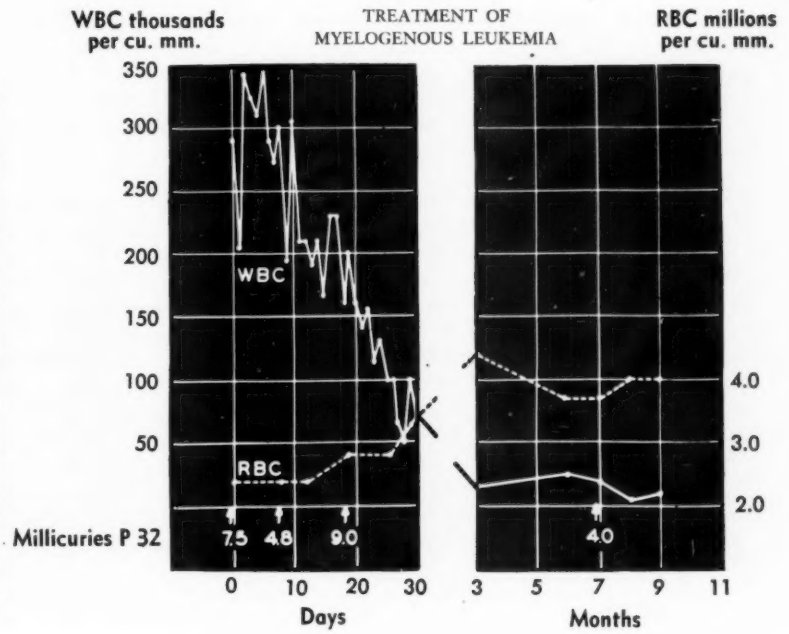

FIGURE 1. Effect of radioactive phosphorus (P^{32}) on the white blood cell count and red blood cell count of a patient with chronic myelogenous leukemia. This patient was one of the earliest ones in the series treated and it is unlikely that the doses of 7.5, 4.8 and 9.0 millicuries every 10 days were actually given, as the estimation of the doses was probably inaccurate. The proper dosage would be 5 to 7 millicuries, followed in one month by a similar dose unless the desired effect had been produced on the blood and general condition of the patient.

All patients with leukemia should be observed carefully at intervals for evidence of infection and proper therapy instituted at the earliest possible moment.

Roentgen ray therapy—It has now been almost half a century since William Allen Pusey introduced the roentgen ray as a form of treatment of leukemia and associated disorders. In this interval, sufficient experience has been accumulated to indicate the proper method of administering this therapeutic agent. Two mistakes have often been made in its use. First, in many instances the dosage has been excessive and consequently not only has the white blood cell count been reduced, but also there has been a drop in the red blood cell count, and sometimes the platelets with an accentuation of the hemorrhagic tendency. Furthermore, the excessive dosage has often caused severe roentgen ray sickness, with nausea and vomiting, loss of appetite and asthenia. With proper adjustment of the dose, however, this may now be averted. Second, in my experience patients were often permitted to relapse too far before roentgen therapy was employed. It is now my practice to consider roentgen ray therapy at any time the patient's white blood cell count exceeds 40,000 per cubic millimeter, provided such treatment has not been given in the preceding six weeks.

It is my opinion that total body irradiation should be used in patients with chronic myelogenous leukemia, except in those in whom the splenomegaly is a conspicuous picture. When the latter condition is present, then localized roentgen exposure should be given to this area. Usually from 50 to 100 r daily or every other day is satisfactory when given locally. When total body or the "spray" form of therapy is used, a daily dose of 15 to 20 r or one given every other day is adequate. Usually the roentgen exposures are given until the white blood cell count reaches the vicinity of 40,000 per cubic millimeter. In chronic lymphatic leukemia, the most effective form of therapy is the localized use of roentgen ray over the enlarged glands or the spleen.

Roentgen therapy is ineffective—in fact, it may be harmful—in patients with the acute and subacute forms of the disease. Furthermore, it is my belief that patients who have chronic leukemia do not become resistant to roentgen therapy in direct relation to the amount previously given. They do become refractory, it is true, but

that is due to the natural progress of the disease rather than to the fact that they have been treated repeatedly. Formerly it was our policy to conserve our treatment on the assumption that only a certain amount of roentgen ray exposures could be given which would be effective and, therefore, that it should not be wasted by giving it periodically and at frequent intervals. This is not true, because the refractoriness develops as a result of the progression of the disease.

Radioactive phosphorus—For over a decade[3] radioactive phosphorus (P^{32}) with a half-life of 14.3 days has been used as a form of irradiation therapy in patients with leukemia. When P^{32} is prepared in the proper form and given intravenously, it diffuses throughout the body but is especially concentrated in the areas of leukemic infiltration in the bone marrow, the lymph glands and the spleen. The marrow also receives an additional amount of irradiation as a result of deposition of phosphorus in bone. This radioactive material emits beta rays which penetrate only a few millimeters. The treatment is sharply localized, therefore, to the areas of leukemic involvement. It is probable that any radioactive element will exert its radioactivity effectively for approximately four times its half-life, or in the case of P^{32} for about 57 days.

In treating patients with leukemia, it has been my custom to give from 5 to 8 millicuries of P^{32} intravenously and then observe the patient for a period of four weeks. If at that time the results are not entirely satisfactory, a second dose of 5 millicuries is administered. As the radioactive material, once injected into the body, continues to act until it is exhausted, it is essential to estimate the accurate dosage as nearly as possible.

Radioactive phosphorus as a form of treatment of leukemia is desirable because of its wide tissue dispersion, its prolonged effect and relatively high selective uptake of the element by the leukemic cells, and the complete absence of roentgen ray sickness. When first used the material was given orally but as complete absorption is uncertain, it is advisable to administer it by intravenous injection. It is of greatest use in patients with chronic myelogenous leukemia but is also effective in the treatment of chronic lymphatic leukemia, but less so in my opinion than localized roentgen ray therapy. Its disadvantages are that it is not generally available, although efforts to correct this are now being made satisfactorily. The dosage is variable and the dangers of overdosage should be kept in mind. Its use is feasible at present only in institutions which have suitable facilities available for handling radioactive material.

Radioactive phosphorus is of greatest use in treatment of chronic myelogenous leukemia and polycythemia rubra vera. It has been used in multiple myeloma with indifferent success. As with roentgen therapy, it is contraindicated in the acute and subacute types of leukemia.

Urethane—Several years ago Paterson and her associates[4] in England reported that urethane (ethyl carbamate) was beneficial in treating patients with myelogenous leukemia. Evidence indicates that it is a mitotic poison which inhibits the rapid division of cells by effecting cellular mitosis. There is no doubt from clinical experience that urethane will depress the bone marrow in patients with myelogenous leukemia. Furthermore, if the dosage is excessive there may be a progression of the severity of the anemia and a pronounced leukopenia and thrombopenia. This preparation is of no use whatsoever in the acute leukemias but has been employed especially in the treatment of chronic myelogenous leukemia and in multiple myeloma.

In patients with chronic myelogenous leukemia, the average total daily dose necessary to induce a remission is 3.0 gm. The drug should be given in enteric-coated tablets of 0.3 gm. (5 gr.) each. The treatment is inaugurated by giving one tablet of 0.3 gm. or 5 gr. three times a day, during or immediately following meals. The dosage should be increased cautiously until the patient is receiving a total of 10 tablets of 0.3 gm. each, a total daily dosage of 3.0 gm. (45 gr.). Usually a beneficial effect is noted within three weeks as shown by a decrease in the total white blood cell count and improvement in the patient's symptoms. Once a satisfactory remission has been induced, a maintenance dose is given which varies from 1.0 to 1.5 gm. a day. It should be kept in mind that patients who are being treated by this drug sometimes have undesirable and excessive depression of the bone marrow and hence the red blood cell, white blood cell and platelet counts should be determined at intervals and the patient remain under the supervision of the physician.

One important objection to the use of this drug has been the nausea and sometimes vomit-

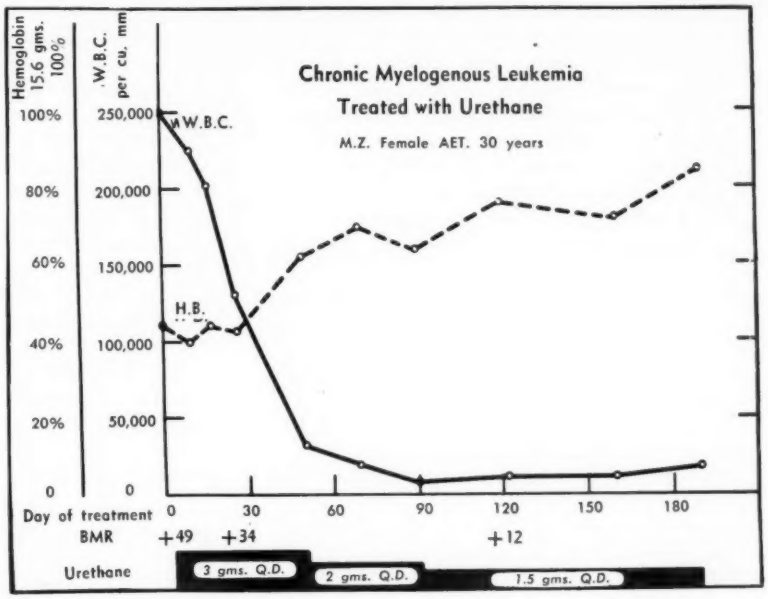

FIGURE 2. Effect of urethane on the white blood cell count and hemoglobin of the peripheral blood in a patient with chronic myelogenous leukemia.

ing which occasionally may be distressing. If this occurs, the drug should be omitted for a day or so or diminished to a level at which untoward symptoms are not produced, and the tolerance then determined. Some patients, however, have been able to take even more than 3.0 gm. a day over a long period without undesirable symptoms. The gastric symptoms when present are usually observed in the first few weeks of therapy.

The drug may be used in patients with chronic myelogenous leukemia who are not evidencing severe symptoms, or it may be employed in conjunction with roentgen ray therapy in an effort to prolong remissions which have been induced by roentgen ray.

Nitrogen mustard—These preparations are derived from mustard gas which was introduced in chemical warfare during the first World War.[5] It is known, among other effects, that they cause a leukopenia when given to animals and consequently this led to their use in patients with leukemia. Nitrogen mustard acts as a cellular poison which exerts its effects on the more rapidly growing tissues, namely those of the blood-forming organs and the gastrointestinal tract. The effects produced resemble those resulting from exposure to roentgen ray and radioactive substances.

Experience has shown that the effect of nitrogen mustard is a purely palliative one but undoubtedly its use will cause an improvement of a patient with lymphoma after roentgen rays have ceased to be beneficial. This is more often observed in patients with Hodgkin's disease and probably is because the intravenous medication reaches involved areas of the body which are inaccessible to the roentgen ray. These preparations produce the most satisfactory results in the lymphoma group, namely Hodgkin's disease, lymphosarcoma, follicular lymphoblastoma, reticulum cell sarcoma, and mycosis fungoides. They are, however, more effective in the generalized form of these diseases. In the localized lesions, the roentgen ray is probably more satisfactory.

The dose of nitrogen mustard which has the composition of methyl bis (B-chloroethyl) amine hydrochloride is on the basis of 0.1 mg. per kilo of body weight. Due to the tendency to produce thrombosis of the vein, the nitrogen mustard is injected into the rubber tubing of an intravenous set through which normal saline solution is flowing. It has been our custom to give such a dose every other day for 4 doses, but in no instance do we permit the total dosage for the four days to exceed 24 mg. There is no evidence to indicate that if this dose is ineffec-

tive a larger one will be of greater benefit. This preparation may cause immediate toxic manifestations, chiefly nausea and vomiting; the reaction, however, is usually brief.

Some investigators have claimed that nitrogen mustards have the ability to resensitize to roentgen ray those patients with lymphoma after they have become resistant to the action of this agent. Furthermore it has been said that those who have become resistant to nitrogen mustard may become resensitized to the drug after a course of roentgen ray therapy. It is possible that these claims may be correct, but such effects have not been observed in my experience. It is safe to conclude that undoubtedly the nitrogen mustards are an effective therapeutic agent in patients with various forms of lymphoma, especially the generalized type of Hodgkin's disease. Furthermore, some benefit may be produced in patients with various varieties of chronic leukemia and in polycythemia, but other forms of treatment appear to be superior in these disorders. Such treatment is contraindicated in patients with acute leukemia.

More recently an oral preparation of nitrogen mustard, TRIETHYLENE MELAMINE, has been introduced which may prove to be effective; however, further experience with this preparation is needed to determine the exact dosage and its value in the leukemias, polycythemia, and in Hodgkin's disease.

Folic acid antagonists—It is known that folic acid is necessary for the growth of certain bacteria and also that it stimulates the growth of cells in the bone marrow. Several years ago it was noted that, following relatively minor changes in the chemical structure of folic acid, a group of substances which have been designated as folic acid antagonists could be synthesized. Although these substances were biologically inert, they were capable of replacing folic acid in the metabolic system which governs the growth of cells. The desired therapeutic effect of folic acid antagonists, however, was to inhibit rather than to stimulate the growth of cells. This led Farber[6] in 1948 to employ such preparations in the treatment of the acute leukemias in children. In this disease which had previously resisted all forms of therapy it was encouraging to note that in about 50 per cent of the patients there was a clinical and hematologic remission which persisted for a few months to a year. Prior to this time there had been no effective form of treatment of patients with acute leukemia. Therefore, although the effects were transient, this constituted a distinct advance in therapeutic measures applicable to the management of acute leukemias.

There are a number of different types of folic acid antagonists, but our greatest experience has been with 4-amino pteroyl glutamic acid or aminopterin, which is as satisfactory as any preparation at present. It is preferable to give the preparation orally but if necessary it may be given intramuscularly or intravenously, in initial doses of 2 mg. for several days, followed by a maintenance dose of 1 mg. or less daily. AMINO AM-FOL is another antagonist which may be given intramuscularly in initial doses of 25 to 75 mg. and a daily maintenance dose of 10 to 30 mg. intramuscularly.

It should be remembered that all folic acid antagonists have severe toxic manifestations and the margin of safety between the toxic and therapeutic dose is not great. The untoward effects which should be known to everyone who employs this form of treatment are of two main types: (1) the destruction of bone marrow with the development of anemia, leukopenia and thrombopenia, and (2) a destructive action on the epithelium of the intestinal tract. This manifests itself by sore mouth, which is one of the earliest symptoms of the toxic effect, and is an indication for the immediate omission of the drug. If it is continued there may be destruction of the cells of the intestinal tract with resultant severe hemorrhage. It is usually possible to avert the toxic manifestations by careful regulation of the dosage, but this requires constant supervision and repeated examinations of the peripheral blood.

From experience with this form of therapy, it can be concluded that, first, in children with acute leukemia it is possible to induce a satisfactory but temporary remission in about one-half the patients. In adults with this disorder there is a similar remission in about one third of the patients. Such a remission may persist for several months. One of the longest I have observed was in a patient treated by us who has now been in a remission for 10 months. Second, the therapy is valueless in patients with chronic leukemia.

The prospect of producing a satisfactory remission in patients with acute leukemia with antagonist therapy seems to be best in those in

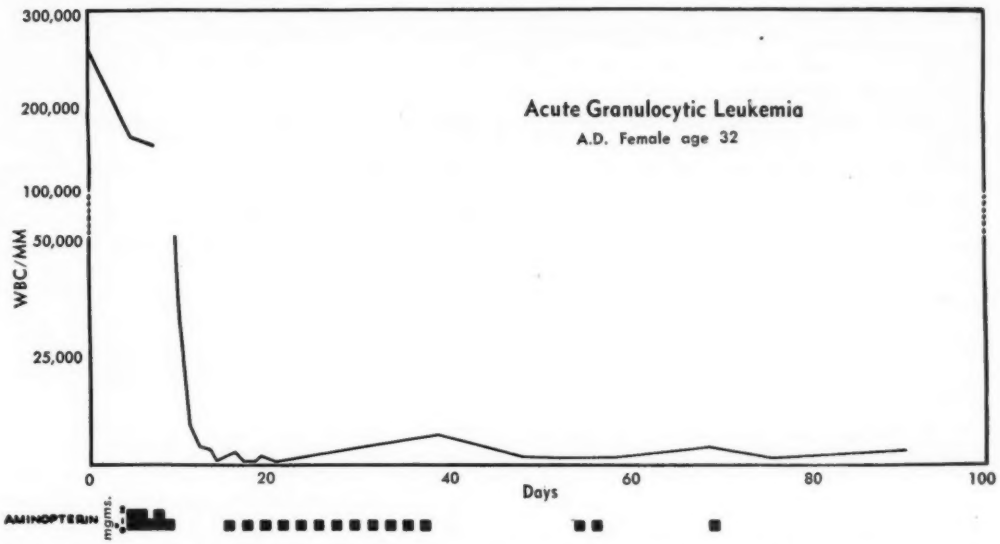

FIGURE 3. The effect of a folic acid antagonist (AMINOPTERIN®) on the white blood cell count when given orally to a patient with acute granulocytic leukemia.

whom the blood and bone marrow are typical of acute leukemia, but in whom the condition is not fulminating and there is no associated extensive bleeding. The prospect of improving the patient also appears to be better in subleukemic states, in young persons, and in the lymphocytic rather than the granulocytic or monocytic types of leukemia. It has been our policy to place the patient on a maintenance dose once a remission has been produced.

In a great majority of patients the remission persists for not longer than six months, at which time a refractory state develops. The basis for the eventual failure of antagonist therapy is not known, but it has been demonstrated by Burchenal and his associates[7] that a strain of leukemic cells in mice that are initially sensitive to folic acid antagonists eventually develop a resistance to this preparation. There is no anatomic basis for this change. If the mechanism for this resistance could be determined and overcome, it would then be the basis for a real contribution toward the therapy for leukemia.

ACTH and cortisone—In recent years it has been demonstrated by Dougherty and White[8] that there is a decrease in the lymphoid tissue in animals following the injection of the adrenocortical substance and, furthermore, such material may induce extreme lymphopenia in these experimental animals. In 1944 Heilman and Kendall[9] showed that injections of Compound E prevented transplantation of rapidly growing lymphosarcoma in susceptible mice and, after the growth had been established, such injections caused retrogressive changes temporarily.

These observations led to the introduction of ACTH and cortisone in the treatment of patients with acute and chronic leukemia of the myelogenous, lymphatic and monocytic types, and in multiple myeloma. Experience is too limited to make a definitive statement in regard to the effectiveness of these two products. It is possible to say, however, that temporary beneficial effects have been observed in some patients. There is evidence to indicate that almost two thirds of the children with acute leukemia will show clinical evidence of improvement following this form of treatment. In about one half of the patients there is definite hematologic remission, which may be complete in some instances and partial in others. The best results apparently are observed in children with acute lymphatic leukemia and next are those with acute myelogenous form of the disease. Monocytic leukemia is the least responsive. Remissions, when they are produced, are temporary and persist for six to eight weeks to several

months. It is possible, however, to induce successive remissions in the same patients as many as three times and perhaps even more by repeated courses of treatment.

It should be kept in mind that untoward symptoms such as those associated with Cushing's syndrome may be observed. Finally, it has been demonstrated that it is possible to induce a further remission in patients with acute leukemia with ACTH or cortisone after they have become refractory to therapy with folic acid antagonists. The possibility arises, therefore, that the combination of folic acid antagonist therapy and cortisone or ACTH may in the future prove to be the most satisfactory form of treatment which has been used in this form of leukemia. Further experience, however, is necessary to establish the accuracy of this statement.

PROGNOSIS

For a long time it has been believed it is not possible to prolong the lives of patients with leukemia. On the other hand, therapy has been considered worth while as it may prolong the useful and comfortable existence of a patient for 90 to 95 per cent of his remaining life. It is generally stated that the average duration of life from the onset of symptoms in patients with either chronic myelogenous or lymphatic leukemia is about 3.5 years.

From my own experience and that of others, there is evidence to suggest that with the more effective use of roentgen ray, radioactive phosphorus, blood transfusions and antibiotics, and possibly the newer forms of treatment, not only will the symptoms be controlled more effectively but also it may be possible to demonstrate that life is actually prolonged. It has been shown by Lawrence and his associates[3] that of 129 patients with myelogenous leukemia treated with P^{32} alone or in combination with roentgen ray, the average duration of life from the onset of symptoms was 3.7 years, with 21 of the patients still living. It is of interest to note that 24 per cent of these patients lived for five years or more and 10 per cent for eight years or longer. Of 100 patients with chronic lymphatic leukemia treated by this same observer and his associates[10] the average duration of life with radioactive phosphorus alone or in combination with roentgen ray was 4.5 years with 24 patients still living. In this group, 35 per cent survived for five years or more and 13 per cent for eight years or more. I am personally familiar with a case of a patient, a physician, who had chronic lymphatic leukemia and survived for a period of 23 years with very little treatment. For the greater interval of this time he was actively engaged in practice without any obvious impairment of his health.

In acute leukemia the duration of life is usually brief, varying from a few weeks to two or three months. Occasionally patients with acute leukemia may develop a spontaneous remission and live longer. The remission rate in acute leukemia induced by folic acid antagonists and cortisone of 30 to 50 per cent, however, is so much greater than that occasionally observed to occur spontaneously, that there can be no question about the effect of these forms of treatment.

The knowledge we have of the prognosis at present, therefore, is encouraging. It is true, however, that no patient with the disorder has ever recovered. Nevertheless, in my opinion the duration of life may be prolonged and the patient live a comfortable existence for a period of years; furthermore, even patients with the most fulminating type of the disease, namely, acute leukemia, may develop a remission as a result of modern therapy. There is a possibility that a cure of leukemia or a treatment which will permit the patient to live for a long period of years in comparative health, while not at hand, may nevertheless become a reality with the further development of treatment.

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Some Practical Pointers About Cross-Eye

EMANUEL KRIMSKY*

NEW YORK POLYCLINIC MEDICAL SCHOOL, NEW YORK CITY

Strabismus or cross-eye is extremely prevalent. Because it often begins in infancy or early childhood it calls for early detection and, if necessary, early management. It is a mistake to defer needed examination or treatment till school age in the hope that "the child will outgrow the cross-eye." Such questions as patching an eye, eye exercises, eyeglasses and surgery are reviewed and analyzed in a practical manner.

The problem of cross-eye is more than an ophthalmologic one for a number of reasons. When it follows birth injuries or even normal deliveries—suggesting a congenital eye muscle disorder—it is primarily an obstetric problem. During infancy and childhood with its contagious diseases and head traumas it becomes a pediatric problem. On the pediatrist and the general practitioner rests the responsibility of deciding whether the child has cross-eye, whether there is a proved relation between a supposed cause and a suspected eye condition, and whether the child should be left alone or be referred to a qualified eye physician for confirmatory diagnosis and treatment.

As the child enters school his eyes assume increased importance. The family doctor's earlier counsels are now reviewed to ascertain whether such preventive measures as corrective eyeglasses should have been recommended at an earlier age. The school doctor and the school nurse now subject this child to vision testing to find, as so often happens, that vision is poor. The ophthalmologist often sees the child only after preventive therapy has been overlooked. At this later stage he will attempt to improve vision and to straighten the eyes by eyeglasses, by surgery or by binocular re-education.

*Adjunct Professor of Ophthalmology, New York Polyclinic Medical School, New York, New York.

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When cross-eye begins in later childhood or in adult life one looks for causes which may be beyond the direct scope of the ophthalmologist. It may then be primarily a neurologic problem because of tumor or injury to the midbrain, or a problem for the internist because of cerebral hemorrhage from severe diabetes or marked hypertension, or for the otologist who sees paralytic strabismus complicating petrositis. Many cases of cross-eye are predestined and inevitable in children of certain families. Even normally there are latent rudimentary evidences of cross-eye not only in persons with straight eyes but also in the fetus, as well as in the animal kingdom. As such, this problem falls within the realm of the comparative anatomist, the anthropologist and the geneticist. The manifold visual disturbances accompanying cross-eye are problems to be solved by the neurophysiologist and the biophysicist.

Cross-eye is not a sporadic problem but one that involves in varying degrees of severity a large percentage of our population. If one includes normal eyes which maintain straightness through everyday stress and strain to overcome latent cross-eye then, like latent tuberculosis, it is normal to have latent cross-eye. Because it is so widespread and diverse in its individual manifestations and in its degrees of severity, careful evaluation and interpretation are required so that the problem case can be wisely

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selected out of this morass of confusion. Only by proper selection and judgment can we physicians contribute to the early care and prevention of this extremely prevalent condition.

WHAT IS CROSS-EYE?

Cross-eye is more than a malposition of an eyeball. It is more than ocular muscle spasm, eye muscle weakness or paralysis. Cross-eye is a complex psychologic, visual, anatomic and physiologic derangement of the delicate binocular mechanism. As a result, the eyes fail to maintain or to attain straightness. Normal straightness of the eyes implies more than a synergistic coordination of all the extraocular muscles. There is also normal binocular vision or bifoveal coordination of the eyes in intimate association with an integrated cerebral fusion mechanism.

The cross-eyed person depends on one eye for seeing while the deviated fellow eye automatically stops seeing or is visually suppressed. That is why one speaks of cross-eye and not of cross-eyes. Such visual suppression may be only momentary and exist while the eye remains crossed. In rarer instances, as in acute paralytic strabismus when the deviating eye has not yet learned to suppress vision as we do when looking in a microscope, the patient is annoyed with double vision which may prove temporary. The cross-eyed individual may not see his eye crossed because when looking in the mirror it may straighten out or, if it happens to remain crossed for this near distance, he may barely recognize his deviated eye through his blurred peripheral visual field as he looks at himself through his straight-seeing eye.

ROLE OF THE GENERAL MEDICAL PRACTITIONER

The general medical practitioner sees cross-eye in its early stages. His examination, though not intended to be thorough, can yield significant information to enable him to decide whether to leave the child patient untreated or whether to consult the eye physician. The mother may call his attention to a turning or to a deviation of the eye in her newborn child which she may have discovered when wiping the lids. Though inspection may show no signs of cross-eye it is usually a wise policy to believe the mother's story unless one can prove otherwise. On early diagnosis and management often depend the fate and happiness and success of a growing child in facing the struggles of living under conditions of possible extreme physical and psychologic handicap. Because cross-eye may remain uncorrected and even lead to marked visual loss it is not a wise policy to assure the mother that "the child will outgrow the cross-eye." The general medical practitioner is in a more fortunate position than the average ophthalmologist to win the friendly attention of the young child by his better trained psychologic approach.

Strabismus may show no change in one person. In another it may change from one moment to the next, or may show itself for one position or direction of gaze and not for another. The eyes may be crossed when looking for near and not for far, or vice versa. To determine whether the eyes are straight or crossed no instruments are required other than an ordinary flashlight for near testing and a 75 or 100 watt lamp for testing for 20 feet. For the near test (Figure 1) the examiner holds a flashlight beneath the master, or preferred, eye to illuminate and to observe the eyes of his subject before him. As the subject looks directly at this flashlight the doctor sees a small highlight on each cornea known as the corneal light reflex or reflection. The positions of the corneal light re-

FIGURE 1. Observing the corneal light reflections for a near test light.

flexes in relation to the centers of the pupils of the eyes determine whether the eyes are straight or crossed (Figures 2A, 5, 7 and 8A).

To determine whether an eye is turned or deviated the examiner first establishes which is the seeing or fixing eye by the central pupillary position of the light reflex in that eye. Then he focuses his attention on the deviating eye which has the light reflex displaced from the seeing position or pupillary center. Displacement of the corneal light reflection from a seeing or central pupillary position in either eye is proof of cross-eye. The light reflection is always displaced opposite to the direction of the deviation. When the reflex is displaced toward the temple in one eye it means that there is a turning-in of that eye, or convergent squint (Figure 7). When the reflection is displaced inward or nasal to the center of the pupil it means that the eye is deviated outward, or the squint is divergent.

The amount of the displacement of the corneal light reflex from the central pupillary position indicates the amount and the degree of strabismus. The patient is tested first with the eyes looking straight ahead at a flashlight which is then shifted to make the patient turn his eyes in different directions. The positions of the corneal light reflexes are studied to determine whether the cross-eye changes or disappears. To ascertain whether the eyes are straight or crossed when looking for far, the child is stood on an office chair and instructed to look at a 75 or 100 watt lamp placed 20 feet away. To observe the corneal light reflexes the examiner lowers his head 13 or 15 inches in front of the patient to enable the light from behind to strike the eyes.

Vision can be tested quite easily in the young child when questioning is impossible. One eye is carefully bandaged to completely occlude vision in that eye. The child is then placed on a high chair and fed, or given a picture book, or allowed to walk or permitted to reach for toys or objects placed at different distances. The responses in the uncovered eye are those noted by the mother at home. For the older preschool child the doctor uses the familiar "E" chart containing the letter "E" in numerous sizes and arrangements and instructs the child to project his fingers in the same direction as the letter which he sees. Charts containing pictures of different sizes are also found useful.

ROLE OF THE EYE PHYSICIAN

The nature of the strabismus is ascertained by the nature of the displacement of the corneal light reflex in the deviating eye as the eyes are made to look at a near test light, a far test light, and then in different positions of gaze. The eyes may be perfectly straight when looking at a near test light and show crossing only when looking for far, or vice versa. Or the eyes may

FIGURE 2. Measurement of divergent strabismus: A. Corneal light reflex displaced nasally in left eye because eye turns out. B. Looking through a rotary prism which reads 30 prism diopters base-in, one sees the corneal light reflex restored to a central pupillary position. This represents the amount of the strabismus.

be straight when looking straight ahead and show deviation only when looking to the side.

When there is strabismus one eye may fail to follow its fellow eye freely when the eyes are made to turn in different directions of gaze. One then looks for muscle weakness or paralysis as the cause of the deviation. The field of gaze showing greatest restriction in movement by either eye provides a clue to the weak or paralyzed muscle, and conversely, the corresponding excessive movement or "upshoot" by the fellow eye indicates the eye muscle which is spastic or overacting. When eyes that are crossed move freely in all directions of gaze one thinks of a central or functional disorder often affecting the divergence or the convergence center of the brain.

A QUALITATIVE measurement of strabismus based on how far the corneal light reflex appears displaced from the pupillary center in the deviating eye is never satisfactory. One cannot prove whether the cross-eye has been reduced or increased by subsequent events or by operation. Accurate measurement of the degree of deviation is therefore necessary for purposes of record (Figure 2). Looking through an ordinary prism placed correctly before the eye one sees the displaced corneal light reflex shifted towards the center of the pupil. The amount of prism required to restore the corneal light reflex in strabismus from a displaced to a central pupillary position represents the amount or the degree of the deviation. Because this light phenomenon is observed through a prism it has been called the Prism Reflex Test.* It is an accurate, controlled, objective method for measuring strabismus.

The displaced position of the corneal light reflex is of further objective value in determining the nature of diplopia when there is paralytic strabismus (Figure 3). The position of the corneal light reflex in the deviating eye in relation to the center of its pupil indicates how the false image is projected from the retina of the deviating eye. If the reflex is displaced outward or temporal it means that the false image is likewise projected outward or temporal or homonymously, as in convergent squint. In the usual nonparalytic strabismus, however, there is no diplopia because vision is suppressed in the deviating eye though vision may be satisfactory in each eye. The strabismus may be alternating in nature and one eye is straight at one time while the deviating eye automatically suppresses vision. Then the deviating eye straightens out to see while the fellow eye now deviates and suddenly stops seeing. This visual suppression is alternating in nature and travels from one eye to the other. When one eye remains constantly

*Krimsky, Emanuel: The fixational corneal light reflexes as an aid in binocular investigation. Arch. Ophth., 1943, pp. 505-521; The effect of a prism on the corneal light reflex. Arch. Ophth. 39:351-370, 1948.

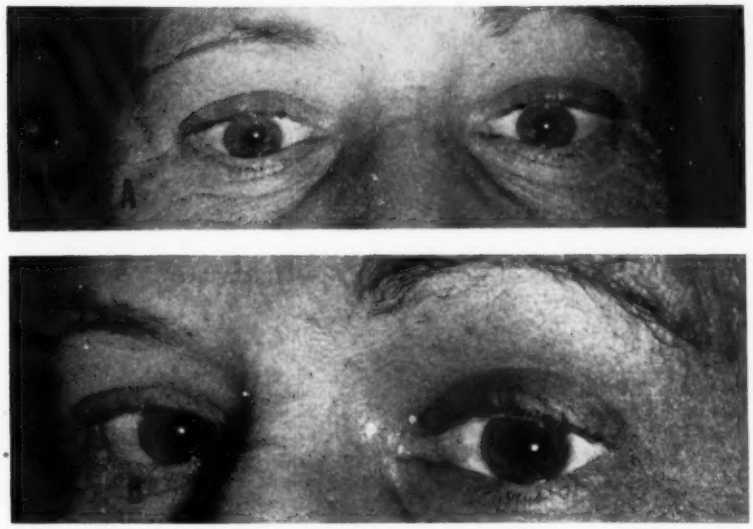

FIGURE 3. Diplopia diagnosed objectively by change in the position of the corneal light reflex: A. In looking straight ahead, the corneal light reflex is centered in each eye and there is no diplopia. B. When the patient looks to the left, the corneal light reflex becomes displaced temporally in the left eye due to failure of that eye to abduct (paralysis of the left external rectus muscle).

crossed it becomes "lazy" or amblyopic and vision may be quite poor in that eye.

REFRACTIVE errors such as hyperopia, myopia or astigmatism are determined objectively by projecting a narrow circular beam of light through the pupil into the retina and observing the nature of the resulting shadow movements as this beam is shifted from side to side. This method is known as retinoscopy. With the aid of trial lenses placed before the eyes one can alter these shadow movements and thus measure the amount of the refractive error (Figure 4). Correction of an appreciable refractive error is often found to straighten the eyes.

Hyperopia is a common factor in convergent squint and the wearing of needed plus lenses not infrequently produces immediate straightening of the eyes as long as the glasses are worn. With marked myopia there may be a divergent strabismus and the wearing of needed minus lenses improves vision, though less often straightens the eyes. Refractive correction improves vision by producing sharp images on the retina, though if an eye has become "lazy" or amblyopic vision may not be much improved.

In convergent squint due to hyperopia, straightening of the eyes is effected by placing plus lenses in front of the eyes to relax accommodation in their crystalline lenses as well as to reduce the impulse to strong convergence or turning-in of the eyes. In divergent squint contributed by myopia such straightening may be helped by placing minus lenses in front of the eyes to stimulate accommodation as well as convergence of the eyes. When the eye accommodates it means that its own crystalline lens becomes thicker in order to see a near object. When accommodation strain is excessive as in hyperopia, plus lenses placed before the eyes relieve the intense effort otherwise required to induce the same optical effect within the human crystalline lens itself.

Normally straight eyes show latent rudimentary evidences of cross-eye. This does not mean that latent cross-eye can lead to manifest or evident strabismus any more readily than normal latent tuberculosis can lead to active tuberculosis. Latent cross-eye is normal when eyes can maintain straightness flexibly by readily compensating for visual stresses and strains. One can induce such cross-eye artificially, however, by upsetting binocular coordination, as by placing a base-down prism before either eye, thus producing double vision. In eyes that are ordinarily straight one now sees a turning-out of one eye, called exophoria; or a turning-in of one eye, called esophoria; or a vertical deviation, called hyperphoria. By studying the positions of the corneal light reflexes, especially in the eye in which displacement of the corneal light reflex

is induced, one can measure with prisms the amount of latent strabismus just as is done for manifest strabismus.

THE QUESTION OF EYESTRAIN

Persons having normally straight eyes as well as cross-eyed individuals complain of discomforts in vision or pains in or around the eyeballs which they describe as eyestrain. The symptom itself is, like headache or backache, meaningless and may not be due to trouble in the eyes but to bodily fatigue, or a debilitating disorder or an imaginary upset. The analysis of the symptom calls for a careful survey to determine accurately whether there is an eye muscle disorder, a refractive error requiring eyeglasses, a cerebral or cranial nerve disorder leading to diplopia or visual field changes, a mental upset requiring psychotherapy, or a systemic ailment. The successful management of the symptom alone will be governed by the training and by the psychologic approach of the examiner to the particular case.

GENERAL CONSIDERATIONS IN MANAGEMENT

Only after thorough examination and evaluation of the entire picture is one in a position to know what treatment to prescribe. The considerations should include:

1. The psychologic makeup of the individual—Is the patient a phlegmatic or a highstrung type? What is his glandular status? Is he a type that would respond to suggestive therapy? Does he have an inferiority complex and does he brood over his appearance or the possible loss of a job?

2. Are there signs of ocular paralysis requiring treatment of the cause? Is the paralytic strabismus due to severe diabetes, marked hypertension, or basal skull injury leading to paralysis, usually of the sixth nerve? Is the ocular paralysis idiopathic in origin and recurrent and due to ophthalmoplegic migraine? Is there evidence of syphilis? Did the ocular paralysis follow lumbar puncture? Is there multiple sclerosis present?

3. Is the cross-eye due to structural damage within the eye leading to visual loss, such as cataract, corneal scar, detachment or other pathology of the retina? This type of strabismus may prove intractable to surgical attempts at straightening.

4. Is there congenital weakness, absence or fibrosis of any of the ocular muscles with preservation of binocular vision in restricted head positions? In congenital involvement of any of the ocular muscles, such as the inferior oblique or the external rectus, vision is often well preserved in each eye. Moreover, the eyes are often straight and binocular vision is normal in the restricted compensatory head positions. Muscle surgery in such cases is often avoided because it may upset the compensating balance which has already been acquired in the restricted head positions.

5. Is the cross-eye due to a congenital imbalance between the convergence and the divergence centers of the brain in which the eye muscles function normally and eye movements are not restricted? Because this type of cross-eye is functional in origin it usually calls for binocular training especially when there is a manifest turning-out of the eye, as in divergence excess or convergence insufficiency.

6. Is there a refractive error which calls for eyeglasses either to improve vision and/or to straighten the eyes? The importance of proper refractive correction cannot be overemphasized. It is the most important single measure in the combined visual and cosmetic correction for many cases of cross-eye.

7. Is the cross-eye part of a systemic condition such as myasthenia gravis? In such cases injection of PROSTIGMINE® often straightens the eyes within a few minutes, though the effect is usually temporary.

In undertaking treatment of the cross-eyed patient one aims to: (a) straighten the eyes as they look in the straight-ahead position both for near and for far, (b) maintain such straightness of the eyes as they are made to rotate in different directions of gaze and (c) restore, if possible, normal vision in each eye as well as binocular coordination or fusion. All these ideals are not often realized and a "cure" is often taken to mean a satisfactory improvement even though there may still be residual evidences of strabismus.

The medical management of strabismus includes such diversified methods as refractive correction of eyeglasses, binocular training not to be confused with so-called "eye muscle exercises," the employment of prisms for training or for comfort, occlusion of the better-seeing eye to force the "lazy" or amblyopic eye to develop better sight, and the treatment of the

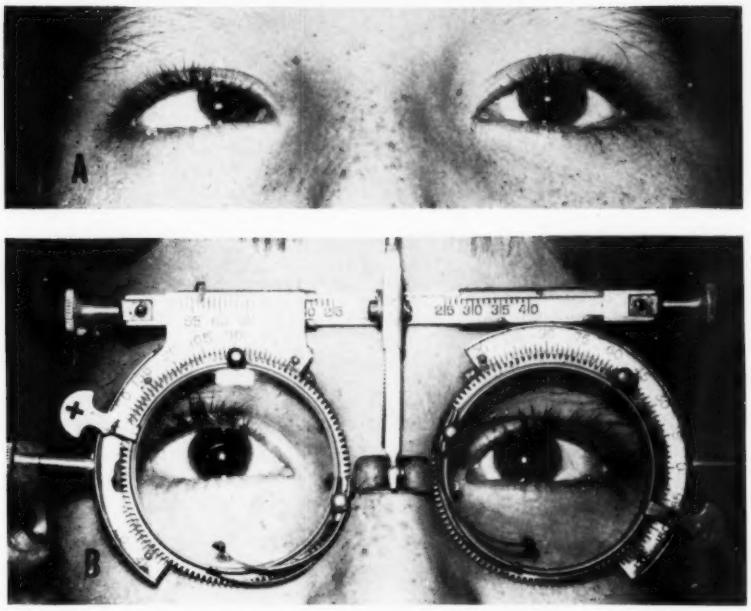

FIGURE 4. The straightening effect by glasses in convergent strabismus: A. Without glasses. B. Immediate effect with trial lenses.

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cause. Even after operation, eyeglasses or fusion training may still be required either to reinforce the benefits from surgery or to complete the straightening effect.

THE PROBLEM OF EYEGLASSES

EYEGLASSES are prescribed to bring visual images to a sharp focus on the retinas. Unlike the camera which has a bellows or extension mechanism to alter focusing for near and for far objects, the compressed eyeball depends on its lens accommodation mechanism which constantly changes the shape of its lens to produce the same focusing effects. In myopia or hyperopia an abnormal effort is placed on this accommodation mechanism requiring an abnormal effort to see clearly. A refractive error is said to exist when an eyeball is shorter than normal or is hyperopic, or when the eyeball is longer than normal or is myopic. A normal-sized eyeball having normal vision without the aid of eyeglasses is said to be emmetropic.

During the growing period of infancy the eyeball is normally shorter or hyperopic, and a greater accommodative effort is placed on its lens to focus visual images sharply. It is this early period in the infant's life which lends itself so readily to the early development of strabismus especially of the convergent type. Realizing that this formative period of infancy is such an unstable one, especially for those with hereditary tendencies, it is fortunate that most children escape the development of this complication. Chavasse* has stated that "it seems highly probable that if glasses were given to an infant immediately and as a matter of extreme urgency at the first momentary glide of the eye, the problem of accommodational squint, both in its visual and esthetic aspects, would disappear." Though this extreme view is not generally accepted it serves notice of the important role which refractive error plays in the early development of cross-eye.

Functional amblyopia or poorsightedness which cannot be improved is often attributed to lack of visual development in early infancy. Theoretically, a pair of glasses prescribed during early infancy should prevent visual disability by relieving the excessive strain on accommodation and thereby sharpening the images on the retinas. In actual practice, however, eye-

*Chavasse, F. B.: Report on orthoptic training. Tr. Ophth. Soc. U. Kingdom 59:495, 1939.

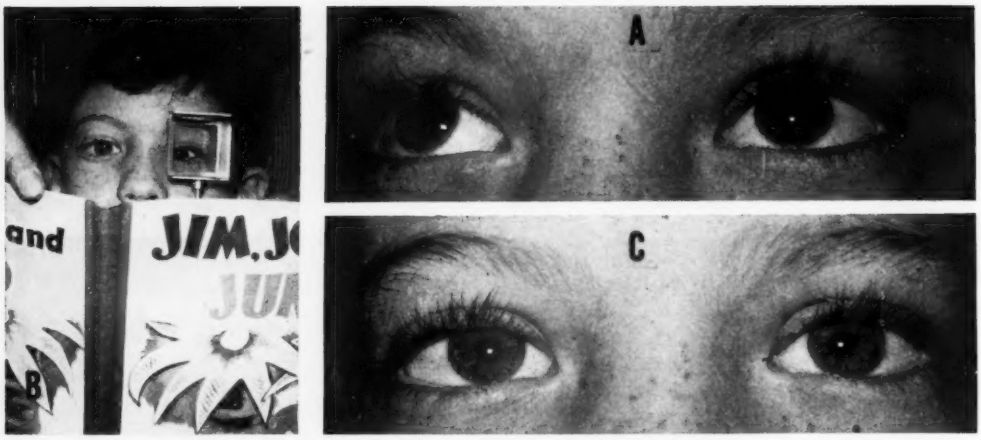

FIGURE 5. The effect of prism training in divergent strabismus. A. Right eye deviated outward and corneal light reflex displaced inward. B. Prism convergence training to counteract turning-out of the eye. C. Eyes straightened.

glasses prescribed for infants of only one year of age can prove too late to restore vision in those who have already failed to develop it. And yet in other instances eyeglasses prescribed during preschool age have restored satisfactory vision as well as straightened the eyes.

When wisely prescribed, eyeglasses are often the most dependable single measure in the positional and visual correction of cross-eye. The benefits from eyeglasses cannot be predicted for the individual case. Fortunately, however, one can often observe the benefits with trial lenses at the time of the examination. The eyes straighten out immediately only to return to the cross-eyed state as soon as the glasses are removed. The patient often sees better. The effects on both vision and eye straightening are not necessarily parallel. Vision may be improved though the eyes are not straightened, or the eyes may be straightened at the expense of blurring vision.

In some instances eyeglasses neither improve sight nor straighten the eyes. And yet even in those apparently hopeless cases glasses may be necessary if only to facilitate focusing of the visual rays on the retinas with the possibility that improved vision will occur spontaneously after some months. When stronger eyeglasses straighten the eyes at the expense of blurring the sight one may have to prescribe two pairs of glasses of different strengths: one which will straighten the eyes, and another which will produce maximum improvement in vision without straightening the eyes. These glasses would be worn at different times to provide a satisfactory combination for work and play as well as for cosmetic correction when desired.

Prisms are often incorporated in eyeglasses to enable one to see binocularly behind such prisms though the eyes are still crossed. Their value is usually limited to chronic diplopia, especially of a vertical nature. Prisms are also prescribed to strengthen binocular fixation and to counteract a tendency of one eye to turn in a certain direction. Prisms are then used to make the eyes pull in the opposite direction. For example, in divergent strabismus with turning-out of the eye, inducing the eyes to turn in with prism often produces gratifying results. Too often, however, prisms are prescribed without reason (Figure 5).

Surgery, as in convergent squint, may be undertaken with the purpose of obtaining only partial correction and supplementing it with corrective eyeglasses to complete the eye straightening, to improve vision, and to reinforce the benefits from surgery. The amount of surgery to be done is often governed by the physiologic responses induced by corrective eyeglasses.

THE QUESTION OF EYE EXERCISES

The term "eye exercise" is misleading and is often used to mean rolling or other energetic movements of the eyes, often for the purpose of "toning" them or for counteracting vague eye complaints. Eyes normally keep moving constantly and automatically to maintain focusing of images on the small retinal foveas.

Natural eye movements are therefore more than just muscle contractions and relaxations, and are reflexly induced by alert-seeing foveas working intimately with the association centers of the brain. Even in cross-eye, one eye moves with its fellow eye.

It is pleasant to think that one could stretch a muscle leading to cross-eye by forcing movements of the eyes in the opposite directions. In actual practice, however, forced eye movements alone are valueless. There is no experimental proof that eye muscles per se can be made stronger by willful turning of the eyes. The word "exercise" has proved such a good selling point that unqualified writers have concocted all sorts of meaningless movements of the eyes to prey on one's credulity and to induce a false sense of security. Eyes keep rotating all the time, even in sleep, and to a sufficient extent for one's everyday needs. There is no proof that any additional parallel eye movements other than those which occur automatically would benefit the eyes.

FIGURE 6. Occlusion of an eye.

BINOCULAR training as distinct from eye muscle movements aims primarily at enabling both eyes to see together in unison. It is combined brain, eye and eye muscle coordination in which eye movements often play but a negligible role. Binocular training concerns itself primarily with simultaneous awakening of both retinas through their sharply seeing foveal spots in these retinas to produce a fusion response. The retinal image, unlike the developed photographic film, is sharp at only one point, the fovea. When eyes are straight, binocular vision is often normal because both foveas are in normal alignment. When one eye deviates, vision in that eye often becomes psychologically suppressed to avoid double vision.

In order to train the eyes to see straight or binocularly for a desired distance, the first aim is to overcome the psychologic suppression in the deviating eye and to make one eye aware of the other. The second aim is to induce by artificial means bifoveal stimulation or fusion in the positions where the eyes are crossed. The third aim is to reinforce such bifoveal fusion and induce the eyes to straighten out.

When one eye is deviated, natural binocular vision is impossible because only one fovea registers a sharp image while the other fovea, because it is out of alignment, receives a different image that is visually suppressed. Fusion can, however, be induced artificially by means of a prism which can bend the light rays so that they will strike both foveas simultaneously. By using a stereoscope with independently moving lighted targets one can also stimulate both foveas by approximating or separating these lighted targets to correspond to the turning-in or the turning-out of the eyes. If the strabismus is divergent it means separating or "diverging" the lighted targets until corresponding images are brought in line with the corresponding foveas. By repeated light stimulation visual suppression is overcome and the eyes soon become aware of two images which they fuse into one. With continued stimulation fusion is reinforced to the extent that when the targets are moved inward the eyes are tempted to follow along in order to maintain fusion. Only through successful bifoveal stimulation can a deviated eye be induced to straighten its position from a long-standing deviation.

The awakening of a fusion response is primarily psychoretinal in nature only through maintained stimulation of the brain and its fusion center via the corresponding foveal points on both retinas. The value of binocular training is most pronounced in cases of divergent strabismus with constant or intermittent turning-out of an eye for near or for far, but in which there is no excessive loss of vision. For these cases, controlled binocular training often proves far more successful than either surgery or eyeglasses because they are psychologic in origin and due to excessive activity in the divergence center of the brain.

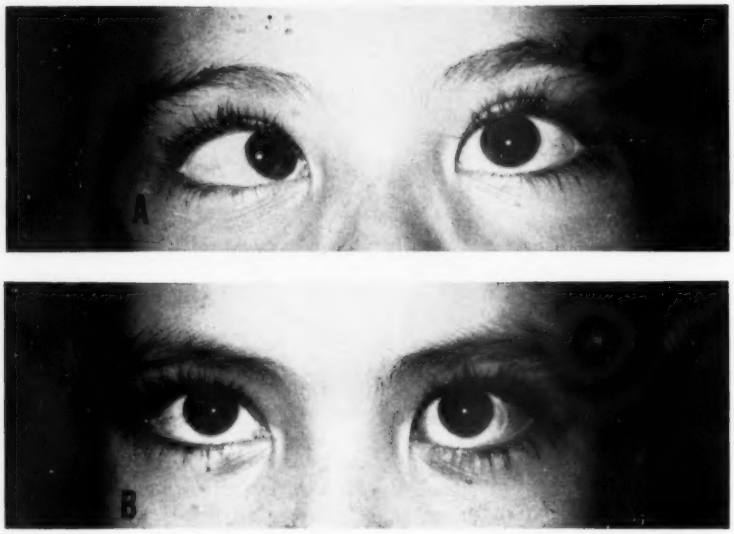

FIGURE 7. Straightening of eyes by surgery.

There is an imperative need for making scientifically controlled binocular training more readily available to the many children who are at present denied such privileges because of financial limitations. A program could be developed first as an experimental project to explore the possibilities of the school and the home for combating visual disabilities connected with strabismus. The school would seem to offer a vast laboratory for combined clinical and psychologic research where daily intensive training could be administered under controlled supervision. An occasional or clinic visit which interferes with the child's daily routine of work and play for the purpose of binocular training usually confers only momentary benefits which cannot have lasting value. Also, the mother is not often made cognizant of the principles involved in training and therefore fails to cooperate wholeheartedly in keeping her child interested.

THE PROBLEM OF OCCLUSION

Many children are seen to wear monocular patches over well-seeing eyes often for months at a time, either to help straighten a crossed eye or to improve sight in an uncovered amblyopic eye. This practice of covering a normal-seeing eye to train an amblyopic or "lazy" eye to see became popular because it was sometimes observed that vision in an amblyopic eye would improve after its normal-seeing fellow eye became blind as a result of injury or disease. Intentional occlusion of a well-seeing eye has therefore been prescribed generously for centuries though there are no reliable statistics, except for an occasional isolated report, to show that the eyes have benefited definitely from such visual enslavement (Figure 6). The use of occlusion has even been extended by the misinformed to that type of cross-eye in which vision is normal in each eye. An eye that is covered must become crossed behind the cover if its uncovered fellow eye has to straighten out in order to focus or to see.

Ophthalmologists are not generally agreed as to the therapeutic value of occlusion. The child may not submit to complete occlusion which is generally agreed to be a prerequisite to possible success. Cases for occlusion may not be properly selected and it is often prescribed in cases of strabismus where vision is normal in each eye and where patching could not reduce the squint but merely transfer the preferred crossing to the other eye. Occlusion to awaken sight in an amblyopic eye is apt to prove dangerous if the child is to depend on that eye for walking and playing. Moreover, it segregates the child from its playmates and may induce an inferiority complex. The benefits from occlusion may prove transitory when the patch is finally removed. Occlusion is probably of some value in the exceptional case. Its value could probably be enhanced if it could be modified to dispense with

FIGURE 8. Congenital aplasia of the left inferior oblique muscle. A. Eyes straight when looking straight ahead. B. Right eye looks upward but left eye fails to follow right eye in its upward movement.

the patch and to keep both eyes uncovered except to partially fog vision in the better-seeing eye without necessarily occluding it. This method of partial occlusion with an attempt to stimulate binocular use of the eyes offers a vast field for intensive clinical and psychologic research.

THE PROBLEM OF SURGERY

THE main reason for surgery for cross-eye is to straighten the eyes when they cannot be straightened by eyeglasses or other conservative measures. A mother will want her child's eyes straightened to shield it from developing an inferiority complex and from becoming an object of sympathy or jibes. An adult will seek straightening of the eyes also to remove an inferiority complex and to feel more secure about his job. Visual improvement following operation is incidental and a fair measure of binocular restoration occurs spontaneously in some of the cases (Figure 7).

There are, on the other hand, some definite reasons for avoiding operation for cross-eye. If there is an acute cranial nerve paralysis as a result of head injury, infection or new growth, one thinks of treating the cause. If the person is happy and comfortable with his strabismus and vision is undisturbed there may be no reason to disturb his state of well-being. If the eye has become structurally and visually damaged as a result of eye injury or eye disease, surgical straightening may not remain permanent. If the cross-eye condition is apparent only when the eyes are turned to one or the other side but are perfectly straight when looking forward, surgery may not prove effective in restoring straightness for all movements of the eyes. This refers especially to such congenital eye muscle disorders as congenital fibrosis of the external rectus muscle (Duane's syndrome) and to congenital aplasia of the inferior oblique muscle (Figure 8). When glasses alone straighten the eyes and even help restore or improve vision it usually indicates that surgery per se would prove physiologically unsound in accomplishing the same beneficial results.

Though eyes are straightened by surgery, the postoperative course cannot always be predicted for the individual case. Physiologic and psychologic influences affect the ultimate results of surgery. The eyes may be straight after operation and remain so for a brief period, and yet after some weeks or months some unexplained readjustment often takes place and the eyes again straighten and remain so permanently. In operating for convergent squint one does not try to straighten the eyes completely but leaves a slight residual deviation in the hope that during the healing and adjustment period, in which needed glasses are worn, the straightening of the eyes will be completed.

Preoperative Evaluation of the Toxic Goiter Patient

WILLIAM P. KLEITSCH*

VETERANS ADMINISTRATION HOSPITAL, LINCOLN, NEBRASKA

Important in the preparation of a patient for thyroidectomy is an accurate, written and, preferably, graphic record of the patient's progress. Although the antithyroid drugs, such as propyl thiouracil, have revolutionized preoperative management of the thyrotoxic patient, the established prerequisites for thyroidectomy must not be abandoned.

KLEITSCH

THE preoperative management of the thyrotoxic patient has been revolutionized by the development of the antithyroid drugs. Without entering into a discussion of the value of propyl thiouracil as a means of producing a permanent "medical thyroidectomy," we feel that the majority of thyrotoxic patients are most rapidly and safely relieved of their symptoms by thyroidectomy.

The preparation of a toxic patient for thyroidectomy is an art which should be acquired by internists as well as surgeons. Not the least important factor in this procedure is keeping an accurate, written and, preferably, graphic record of the patient's progress. The written record is absolutely essential because memory alone will not suffice to record the necessary response to treatment, which is the most important element in deciding the optimal time for operation.

Cole and Fowler have made the plea that established prerequisites for thyroidectomy not be abandoned with the use of antithyroid drugs. This point cannot be overemphasized. The fundamental requirements for safe thyroidectomy are still the same, regardless of the method used to prepare the patient. The use of antithyroid drugs introduces the element of myxedema and the possibility of leukopenia; it does not eliminate the need for rigid preoperative requirements. The preoperative use of such drugs has complicated rather than simplified preoperative care, despite the fact that their use has markedly reduced operative mortality. This might be compared with almost any new treatment, for instance blood transfusions. Transfusions are often lifesaving but the use of them introduces many hazards such as reactions, hepatitis, etc.

The criteria suggested by Cole as a prerequisite for thyroidectomy are: (1) a resting pulse rate of less than 110, (2) a basal metabolic rate of less than +50 per cent, (3) a gain in weight and strength and (4) treatment of all complications. In our experience we have varied from these criteria only in making them more rigid. We prefer to see the pulse rate less than 100 and can usually restore it to a rate somewhere in the 80's. We do not operate on a

*From the General Surgical Service of the Veterans Administration Hospital, Lincoln, Nebraska. Dr. Kleitsch is now chief of surgical service at the Omaha Veterans Administration Hospital.

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patient whose basal metabolic rate is over +30 per cent but we do not like to see it fall below +10 per cent. Like Cole, we feel that a gain in weight is the most important single criterion of control of toxicity. In order to establish a rule for gain in weight we demand that the following be accomplished before thyroidectomy is considered safe: a basal weight line is established and it is required that the gain in weight be 10 pounds over the basal weight *plus a straight line increase* (on the weight graph) for five days.

Antibiotic drugs form a useful adjunct in preoperative planning to eliminate infections and strenuous efforts are made to control cardiac insufficiency if present. Eliminating technical errors and errors in judgment, the only real remaining danger in thyroidectomy is an acute cardiac accident (acute failure, ventricular fibrillation). These are, fortunately, rarely encountered and the mortality rate of thyroidectomy should now be considerably less than 1 per cent.

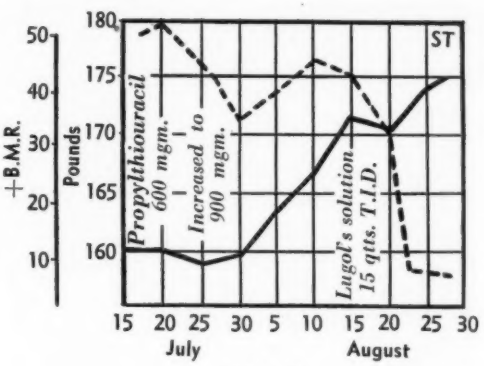

FIGURE 1 *(Case 1).*

DIFFERENTIATION OF THYROTOXICOSIS AND NEURASTHENIA

It has been recommended that symptomatic improvement following the administration of iodine suggests that symptoms are organic rather than functional in nature. We cannot agree with this concept since medical attention and the administration of a drug (iodine) will reassure and comfort the neurotic as well as treat the toxic patient and, therefore, will give symptomatic relief in both conditions. Acute anxiety is the condition most often confused with mild thyrotoxicosis and this is exactly the neurotic manifestation which most readily responds to reassurance. To differentiate these two conditions we prefer to apply our therapeutic test to the neurosis.

To rule out the effects of anxiety the patient is hospitalized, a daily weight graph is established and the basal metabolic rate is taken twice weekly. He is seen and examined by a physician twice daily, vitamins are prescribed and a regular diet is ordered. The patient is ambulant and kept busy about the hospital either in occupational therapy or acting as a nurse's aid. Oral assurance is given by the doctor and possibly a small sedative is administered; iodine and antithyroid drugs are avoided. If, under this routine, the patient improves symptomatically and gains weight, thyrotoxicosis can be eliminated from the diagnosis. This regimen will not improve the symptoms of a toxic patient and he certainly will not gain weight on it. We feel that this routine will effectively rule out thyrotoxicosis; it will not, however, rule out all types of psychoneurosis; i.e., not all types of psychoneurotics will improve symptomatically. It will most effectively eliminate anxiety, but mixed psychoneurosis may not respond (especially depressive states).

GENERAL EVALUATION

The overall evaluation of a thyrotoxic patient is an art which cannot be learned by reading. It is learned at the bedside and from a preceptor. Experience and careful study of the patient are indispensable. One may, however, record some of the observations that the clinician attempts to make.

The deportment and attitude of the patient are significant. The hyperactivity of the toxic patient is supported by evidence of a fine fibrillary tremor of the hands and often of the tongue. Purposeless activity is often present. Despite this activity the thyrotoxic patient is usually fairly well composed emotionally and displays little evidence of anxiety. Psychoneurotic tendencies may be present in varying degrees and are most often expressed as emotional instability and anxiety. The neurotic toxic patient is introverted and his anxiety is focused upon his goiter and his physical condition. The introversion is manifested by sensations of choking and fullness in the neck. Whereas the thyrotoxic patient will become more composed as the effect of propyl thiouracil and iodine be-

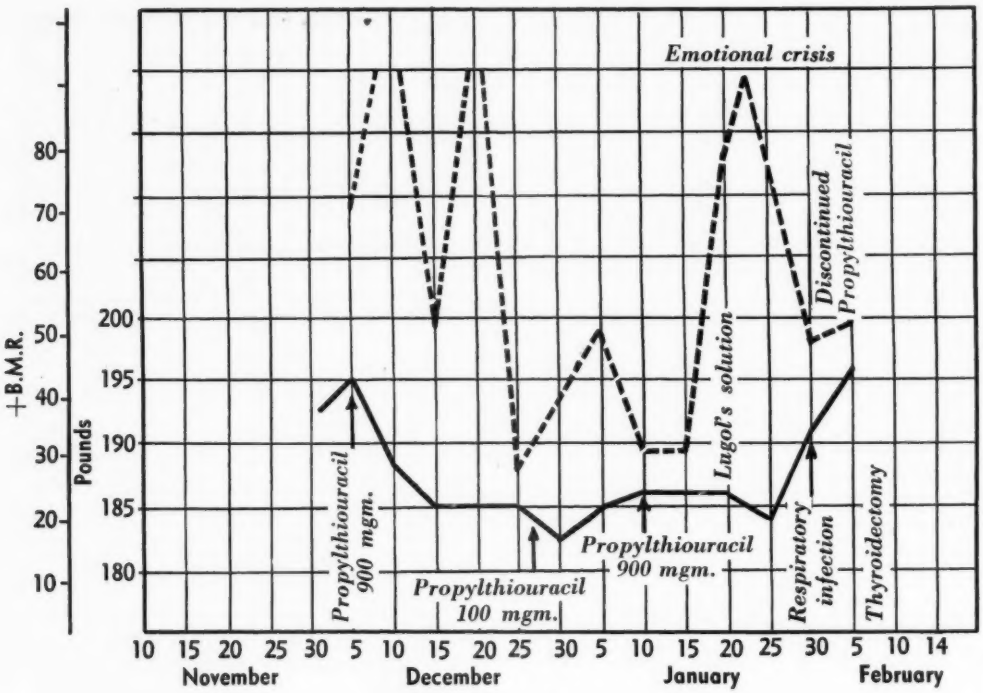

FIGURE 2 *(Case 2).*

comes apparent, this is not true of the patient who has superimposed neurotic traits. The hyperactivity will regress in the former and he will calmly await surgery. The neurotic will also lose much of his hyperactivity but his anxiety will remain the same or even get worse. The fine tremor may be replaced by a coarse tremor. The anxiety is reflected in a continuing concern over his condition, difficulty in accepting the need for a preliminary period of preparation before thyroidectomy and the need for constant reassurance. The basal metabolic rate may be extremely confusing in this type of individual. Emotional episodes will periodically elevate it and, in general, all basal metabolic readings will be found to be high.

Palpation of the skin will also contribute significant findings. The skin of the chest, over the sternum, is characteristically hot and wet in the toxic patient. As the toxicity is reduced the skin becomes cool and dry. This is an important element in the clinical appraisal of thyrotoxicosis. Sweating is also a frequent finding in anxiety states but there is a significant variation from the sweating of thyrotoxicosis. The sweat of thyrotoxicosis is diffuse, most severe over the body and always associated with a hot skin. The sweating of a neurotic is profuse, usually beaded, and most severe on the face and hands. The skin is usually cool and the chest is often dry.

The appetite is good and the only difficulty the toxic patient has is getting enough food to satisfy it. Only in crisis is the appetite lost. Poor appetite in a thyrotoxic patient not in crisis, again, is usually a psychoneurotic phenomenon. The following cases have been selected as examples of the preoperative study and preparation of thyrotoxic patients. The use of a combined basal metabolic rate and of a weight graph is indicated.

CASE REPORTS

Case 1 (Figure 1)—This 37-year-old white male had typical signs of an exophthalmic goiter with moderate toxicity. The graph illustrates a typical, satisfactory response to propyl thiouracil, which was started as soon as the basal metabolic rate was established. The immediate loss in weight is a fairly typical phenomenon and seems to be associated with the loss of ap-

petite incidental to the emotional stress in the period of adjustment to hospital routine and in anticipation of an imminent operation. This man was given a maximum of 900 mg. of propyl thiouracil daily (in 3 doses). The gain in weight was steady.

After the patient had gained 10 pounds over his admission weight, it was felt, on the basis of a clinical estimation of his appearance, that he was approaching operability. He was therefore given Lugol's solution, administered in a 15-drop dose three times a day. The basal metabolic rates showed a satisfactory response to this combined therapy and he was operated upon 47 days after first applying for treatment. This is considered to be a simple, uncomplicated response to treatment and is the type that we expect to find in the average toxic goiter patient.

Case 2 (Figure 2)—This 44-year-old white male veteran was a rather unusual toxic goiter patient. He was a large man, weighing 200 pounds and measuring over 6 feet in height. In addition, he had an enormous goiter. There was no exophthalmos but the toxic symptoms were marked. There also was a pronounced emotional instability, which almost amounted to a disturbed state. The basal metabolic rates of +108 and +95 reflect the psychoneurosis rather than the toxicity of the gland. It will be noted, from a study of the graph, that the true basal metabolic rate was probably between +60 and +70. The usual immediate drop in weight occurred and was found to be rather pronounced, as one would expect in a person who is emotionally disturbed. Propyl thiouracil was given (900 mg.) daily with relatively little immediate effect upon the weight.

Lugol's solution again was given when the clinical evaluation indicated that the toxicity was under control and the patient would soon be ready for operation. Notice the pronounced effect upon the basal metabolic rate by the emotional crisis which was precipitated when his wife notified him of the sudden death of his father-in-law. It is significant that this elevation in basal metabolic rate was not evanescent but actually lasted at least a week. When toxicity was finally controlled, the straight line increase in weight, as depicted upon the graph, was dramatic.

FIGURE 3 *(Case 2).* Photograph of surgical specimen giving some indication of its enormous size. The glass tubing is a centrifuge tube.

The postoperative examination of the excised goiter

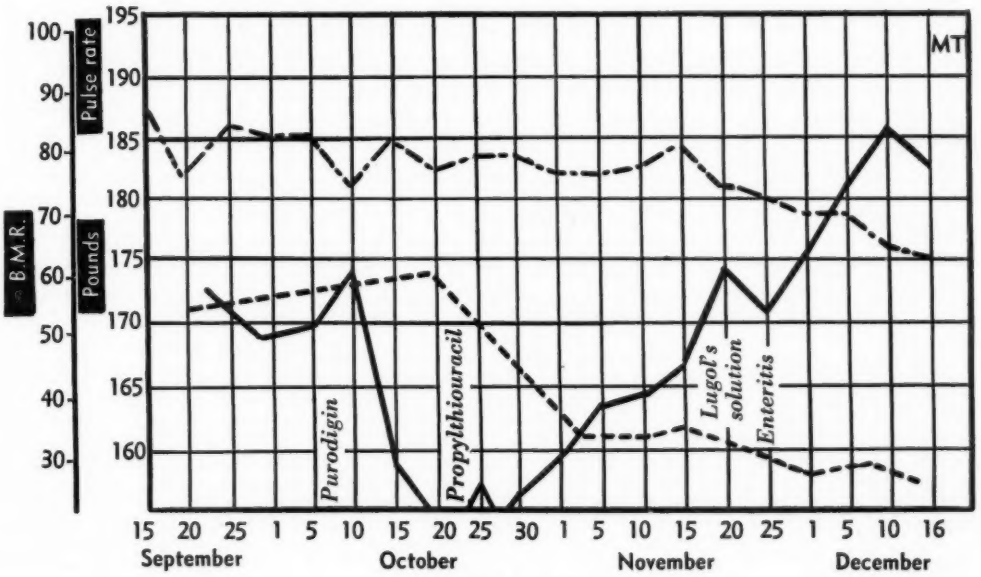

FIGURE 4 *(Case 3).*

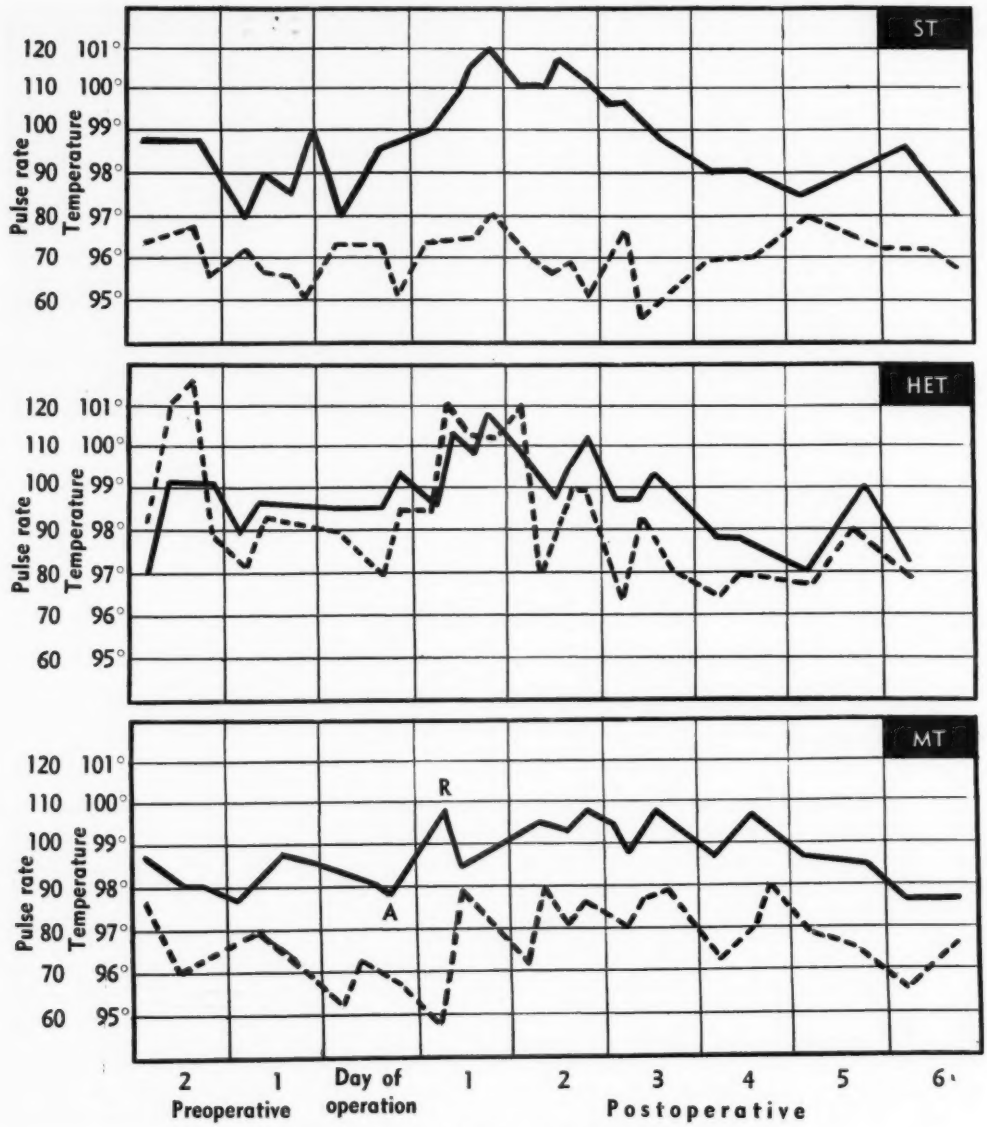

FIGURE 5. Composite graph of thermal and pulse responses to operation.

revealed why the preoperative period of preparation was so long. The thyroid gland was diffusely enlarged and truly enormous, weighing 322 gm. (Figure 3). It has been suggested that large toxic goiters will require relatively larger amounts of propyl thiouracil over a longer period of time to control.

Case 3 (Figure 4)—This 51-year-old white male veteran represents a complicated and difficult problem in preoperative evaluation of thyrotoxicosis. The man was psychotic (dementia praecox) and in cardiac decompensation. The psychosis was important only in that a history was difficult, if not impossible, to obtain. The goiter was small, weighing only 67.5 gm. after thyroidectomy.

The pulse curve is superimposed upon the chart to indicate how much less reliable it is, as an index to operability, than the weight curve. The basal metabolic rates indicate a rapid response to propyl thiouracil. The psychosis was associated with a placid emotional

state which did not affect the readings. The weight curve is most interesting. Notice the precipitous drop following the administration of PURODIGIN. This is due to loss of water (edema) as cardiac compensation is restored and diuresis occurs. After digitalization was accomplished, a true basal weight line was established and the gain in weight now represented actual tissue weight gain—forming an almost straight line increase.

It will be noticed that the gain in weight was carried considerably beyond what we consider to be a safe gain in weight. This was due to the patient's psychotic state which made a clinical evaluation of his thyrotoxicosis difficult. He was, therefore, given the benefit of the doubt and was treated preoperatively somewhat longer than normally. The preoperative period was also prolonged by the development of a gastroenteritis associated with diarrhea on November 22, and represented on the graph by a second, but smaller, precipitous drop in weight.

HAVING indicated the use of the combined weight and basal metabolism graph in the preoperative study of toxic goiter patients, we are presenting comparative graphs of the response to surgery (Figure 5). This graph represents the temperature and pulse curve of all 3 cases, for two preoperative days, the day of surgery and the first six postoperative days. It will be noted that the alterations in the pulse rate are minimal. The thermal reaction to the operation is likewise minimal. These patients are usually discharged between the fourth and seventh postoperative days. No medication of any kind is given after discharge from the hospital as it has not been found necessary.

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1. COLE, W. H., and FOWLER, E. F.: The Present Status of the Surgical Treatment of Hyperthyroidism. Charles C Thomas, Springfield, Illinois, 1948.

COVER PAINTING HIGHLIGHTS THYROID GLAND

THE TREATMENT of diseases of the thyroid gland is a multifaceted subject including, separately and in combination, medical and surgical procedures. In his cover painting, *Postgraduate Medicine* artist Edmund Kopietz has presented a composite study of medical treatment centering about an anatomic representation of the normal thyroid gland.

Many persons have contributed to an understanding of the functioning of the thyroid gland and to the development of therapeutic agents used in treating diseases of the gland. Mention should, however, be made of the man who first demonstrated the therapeutic value of iodine in the treatment of goiter—Coindet in 1820.

The physiologic action of the thyroid upon various functions of the body is far-reaching in its effects; it acts on the basal metabolism; growth; the nervous, muscular and circulatory systems and the other endocrine glands.

In the elements of the drawing may be seen the different sources from which are obtained thyroid extract (the sheep), the all-important iodine (kelp and lobster from the sea), and the latest weapons in the armamentarium of thyroid therapy—radioactive isotopes.

Reprints of the cover, mounted and ready for framing, are available on request to *Postgraduate Medicine*, 516 Essex Building, Minneapolis 3, Minnesota. Price: $1.00.

Diagnostic Clinic

Thyroid Disease Today

FRANK H. LAHEY*

LAHEY CLINIC, BOSTON

Newer developments in the management of patients with toxic goiter, exophthalmic goiter and discrete adenocarcinoma of the thyroid, including clinical signs pertinent to establishing the proper diagnosis, are presented in this diagnostic clinic. Preoperative care and antithyroid agents are also discussed.

I WOULD like to present 2 cases of toxic goiter; there was a third patient to come, a case of discrete adenoma, but if there is time I can speak about discrete adenoma without showing that patient. I would like to speak of some of the fundamental things in regard to hyperthyroidism—how the various methods of treatment act, such as the antithyroid agents and radioactive iodine; something of the basic physiology of the thyroid and something about the metabolism of iodine.

Let us consider first a young lady who has all the symptoms and findings that should identify her condition to anyone as diffuse toxic goiter. She has a large, irregular gland, she has lost weight, her menstrual periods have changed, she has tachycardia, she feels the heat, she has an increased appetite and she originally had a basal metabolic rate of +63. She has been on propyl thiouracil, however, and her metabolic rate is now down to +19.

The second young lady has primary hyperthyroidism or exophthalmic goiter. She has all of the same symptoms but to a more intense degree, because she has not been on propyl thiouracil but has been given iodine for eight or nine months. The appearances of these two girls represent the differences between these two agents. Propyl thiouracil, if given in large enough doses and long enough, will bring the metabolic rate to normal and, if its administration is continued, even to below normal, while iodine will control a portion of the disease but will not control it completely.

The girl who has been given iodine has all the same symptoms that the other girl has. She is nervous and apprehensive, she has lost weight, she has tachycardia, her skin is definitely moist, and if you could see them at close range you would see that she is definitely more activated than is the girl who has been given propyl thiouracil and had her metabolic rate brought from +63 to +19.

I would like to speak of a few of the clinical signs of hyperthyroidism which aid in making the diagnosis. I never see a patient suspected of having hyperthyroidism without running the palm of my hand over the back of the arm. If he or she has a marked increase in metabolism there will in most instances be a velvety feeling to the skin out of all proportion to the smoothness that can be felt in nearly everyone's skin. The increased radiation of heat and moisture gives the skin the velvety character which is quite perceptible on touch.

You all know how to palpate thyroid glands

*Director, Lahey Clinic; Surgeon, New England Deaconess Hospital; Surgeon-in-Chief, New England Baptist Hospital, Boston, Massachusetts.

Presented at the thirty-fifth annual Assembly of the Interstate Postgraduate Medical Association, Chicago, 1950.

so that you can feel them through and through. I have many times demonstrated it, but I will repeat the principle. The chin is turned to the side of the lobe which is to be palpated to relax the sternomastoid on that side; the larynx is dislocated to that side by pressure on the opposite side of the plate of the thyroid cartilage. The finger is then placed behind the sternomastoid and the thumb over the gland in front; as the patient swallows, the gland can be palpated quite satisfactorily to determine its consistency, firmness and nodularity. Firmness is an important point in a patient suspected of hyperthyroidism because, as I will mention in discussing some of the fundamental physiology of the thyroid, the excessive production of thyroxin can be produced only by a gland which is hyperplastic. Hyperplasia in a thyroid gland produces the firmness. Therefore, in borderline cases of hyperthyroidism, the clinical feature in favor of hyperthyroidism is the firmness of the gland. The only two conditions with which firmness in the glands can be confused are malignancy, which is usually localized, and thyroiditis, which is diffuse and involves all of the glands but is usually of such stony hardness that it is not confused with the hyperplasia of hyperthyroidism.

When you look closely at the girl who has had Lugol's solution, you will see something that also is of value in making a diagnosis of hyperthyroidism, that is, moisture on her forehead caused by excessive heat radiation secondary to the high metabolism. If you have her hold out her hand and compare it with that of the other girl, you will find that she has a very definite tremor, much more obvious than is the tremor of the girl who has been on propyl thiouracil.

The girl who has been given propyl thiouracil is practically ready for surgery; another week or two will bring her metabolic rate to normal. The other girl should be put on propyl thiouracil until her metabolic rate is brought completely to normal and all her toxic symptoms have disappeared; then she will be ready for surgery.

I will now discuss some of the fundamental features of hyperthyroidism. They should be understood so that we all have a good concept of how the thyroid gland functions, how thyroxin is either underproduced or overproduced. If these fundamental features of hyperthyroidism are understood, I can explain quite clearly how some of the newer antithyroid agents and radioactive iodine function.

FRANK H. LAHEY

THE basis of thyroid activity, not unlike the basis of adrenal activity, is the pituitary-thyroid axis. Adrenal activity may be demonstrated by many things, perhaps best by pheochromocytomas with the associated paroxysmal hypertension. The basis of activity in a thyroid case is related to the pituitary-thyroid axis and in an adrenal case to the pituitary-adrenal axis.

The fundamental occurrences that produce hyperthyroidism can now be stated quite clearly. There arise stimuli in the hypothalamus, in the supra-ocular and paraventricular nuclei which promote activity in the anterior pituitary, thus creating an excessive output of thyrotropic-stimulating hormone. The thyrotropic-stimulating hormone results in hyperplasia of the thyroid gland and the hyperplasia of the thyroid gland results in the excessive synthesis of thyroxin.

Thyroxin is manufactured by the combination of iodine and tyrosine to produce diiodotyrosine, but iodine in the thyroid gland exists not in the free form which is necessary to com-

bine with tyrosine in order to produce diiodotyrosine, but in the form of an iodide. There must, therefore, be a factor within the thyroid gland which is capable of liberating iodine into a free form. This factor is suspected of residing in the epithelial cells lining the acini and is the result of an enzymatic process called the peroxidase process. Diiodotyrosine is created by this combination and the final synthesis into thyroxin probably takes place within the colloid within the acini. If one understands from this somewhat oversimplified explanation how thyroxin is produced, it can further be understood that when excess thyroxin is produced, it in turn has the capacity to depress the activity of the anterior pituitary and so diminish the output of thyrotropic-stimulating hormone. This, then, is the circular effect in the relationship between the pituitary and the thyroid which has been termed the pituitary-thyroid axis.

We have always known that hyperthyroidism is related to emotional state. While obviously we cannot trace the direct effect of the emotions upon the hypothalamus and so on to the anterior pituitary, then to the thyroid, this does quite satisfactorily link up the physiologic facts with what has been suspected over the years. The thyroid functions normally when there is a coordinated relationship between the anterior pituitary and the thyroid; when there is a little too much thyroxin, the output of thyrotropic-stimulating hormone is diminished and vice versa. Why there should occur the occasional rampant effect of thyrotropic-stimulating hormone without the depressing effect, no one has yet explained.

All of these features can be illustrated very simply by what happens to the epithelial acinar thyroid cell in these various states. The normal epithelial cell lining the thyroid acinus is cuboidal in character, but as soon as an excess of thyrotropic-stimulating hormone affects the gland, this cell becomes the high columnar overactive type of cell. Likewise when this high columnar cell which characterizes the hyperplasia of hyperthyroidism occurs in a patient who is given Lugol's solution, there appears the change which has been termed involution, by which the high columnar cell is converted not even into a cuboidal but into a low, flat cell so characteristic of the involution which follows the employment of Lugol's solution.

Dr. de Robertis, working at the Massachusetts Institute of Technology, has been able by a quick-freeze method to make slides of the thyroid cells of a rat at various intervals after injecting pituitary thyrotropic-stimulating hormone. He has been able to show the migration of colloid from the acini through the acinar cell directly into the capillaries lining the periphery of the thyroid acinar cell by direct permeation of the capillary walls. One can see in these cells in a normal rat a limited number of colloid droplets, which are the vehicles for thyroxin, being extruded into the capillaries around the epithelial cells. In experimental hyperthyroidism in the rat which is produced by the injection of an excess of thyrotropic-stimulating hormone, these droplets are greatly increased in number and extruded at many points through the walls of the capillary into the blood stream to bring about the effects of an excess of thyroxin which is, of course, the mechanics of the production of hyperthyroidism.

Two groups of agents are now recognized as interfering with the synthesis of thyroxin, the thiouracil group and the sulfon group. It is probable that the thiouracil group affects the synthesis of thyroxin by interfering with the peroxidase process which has the ability to liberate free iodine, thus permitting its combination with tyrosine to produce diiodotyrosine and so to be synthesized further on into thyroxin. It is probable, since thyroxin is formed within the colloid, that the sulfon group affects the further synthesis of diiodotyrosine into thyroxin while it rests in the colloid within the acini. This is the fundamental basis of the treatment of hyperthyroid patients with antithyroid agents. An example of the first group is an agent that everyone knows, propyl thiouracil or methyl thiouracil, and of the sulfon group, aminothiazole.

THE principle of the affinity of the thyroid gland for iodine is the basis of treatment of thyroid disease by irradiated iodine. Irradiated iodine is selectively taken up by the thyroid as was shown a good many years ago in thyroid slices by Rabinowitz of Montreal. It is carried to the thyroid cell and deposited in the colloid within the acinus. By irradiating iodine, it is possible to convey this irradiated iodine into the colloid so that the irradiation bombardment of the epithelial cell lining the acini is really from within outward, and so, particularly in hyperthyroidism, very effectual in bringing about the destruction of the acinar cells which make pos-

sible the synthesis of thyroxin. The reasons that irradiated iodine is less effectual in toxic adenomatous goiter than in primary hyperthyroidism are that the acini in toxic goiters are much larger, the amount of colloid within the acini is very much greater and so the radiation concentration is much more dilute and thus less effectual in these larger acini than in the smaller, largely colloid-free acini, which occur with the hyperplasia of hyperthyroidism.

All of this fundamental physiology is borne out by what goes on in the patient with hyperthyroidism who is given an antithyroid agent. What happens is that the thyroid does not manufacture thyroxin, and so no thyroxin is available to depress the anterior pituitary, with the result that it continues to pour out the thyrotropic-stimulating hormone to produce hyperplasia within the gland in a fruitless endeavor to manufacture thyroxin. It cannot manufacture thyroxin because the important element with which thyroxin is synthesized, iodine, has not been liberated from its iodide form.

Because of this persistent histologic picture of hyperthyroidism we have always thought that these antithyroid agents would not prove of real worth in bringing about a permanent remission in the disease as has now, I think, largely been accepted as true. We believe the antithyroid agents possess their real value as a method of temporarily reducing the metabolic rate in order to get patients ready for surgery, because if you operate upon a patient whose metabolic rate has been brought to normal with an antithyroid agent, you will still find microscopically the hyperplasia in the gland so characteristic of hyperthyroidism.

We have often reported that the hyperplasia found in the patient with hyperthyroidism whose metabolic rate has been brought to normal with the antithyroid agent makes operating conditions of the gland technically even worse than they used to be in patients with exophthalmic goiter operated upon in the pre-Lugol days. The thyroid gland is so friable and so vascular in such patients that it is technically almost impossible to deal with it. For that reason we suggested early in our experience with the antithyroid agents that this gland be converted into a firm, avascular, tough gland by involuting it with Lugol's solution, which, as stated above, will occur when this drug is administered. That is the reason Lugol's solution is employed in the last two weeks of preparing these patients for subtotal thyroidectomy.

TABLE 1

ANTITHYROID DRUGS OF CHOICE

DRUG	DAILY DOSAGE, MG.*	INCIDENCE OF REACTIONS (PER CENT)
1. Propyl thiouracil	200-400	1.6
2. 1-methyl-2-mercaptoimidazole (TAPAZOL)	20-40	3.0

*Administered as a divided dose twice daily at 12-hour intervals.

Let me say just a few words regarding some of our experiences with these cases, because I am able to bring to you perhaps as large an experience as there is on the preparation of patients with hyperthyroidism for surgery with the antithyroid agents. We have now prepared and operated upon 2100 hyperthyroid patients, preparing them with one of the various antithyroid agents, thiouracil, THIOBARBITAL,® propyl thiouracil, methyl thiouracil, aminothiazole and 2-mercaptoimidazole. With this large experience with the various agents, we have been able to determine which is the safest and which is the most satisfactory.

We have abandoned thiouracil and thiobarbital because of the large incidence of complications associated with them. We rarely use methyl thiouracil now, because of the high incidence of complications with it (13 per cent). Aminothiazole produces nausea. We have now prepared over 1200 patients with propyl thiouracil, and have concluded that it is the safest and the most satisfactory of all the agents. 2-Mercaptoimidazole has not been used long enough so that we can definitely state its percentage of complications and its effectiveness (Table 1).

We used to hear that if the agent (thiouracil at that time) was given long enough a permanent remission could be brought about. We have learned that the length of time that the antithyroid agents are employed is no indication of the likelihood of their bringing about a permanent remission. We see patients almost daily who have been given the agent for three years and upon abandoning it have promptly gone into a state of hyperthyroidism. We feel very strongly that the place of the antithyroid agents is being more and more accepted as that of getting toxic patients nontoxic in preparation

for surgery. The prolonged administration of propyl thiouracil is more and more being demonstrated as exposing the patients to needless risk of complications, needless expense by constant medical supervision and needless delay in being restored to a permanently normal state by an adequate subtotal thyroidectomy.

Many physicians ask us what we do with the patients who are resistant to the antithyroid agents, and in whom the metabolism cannot be brought to normal. We have never had that experience. We can bring the metabolic rate to normal in all cases if we give enough of the agent, give it long enough and do not combine it with iodine, because iodine interferes with the effectualness of the antithyroid agent in terms of the rapidity of descent of the metabolic rate.

In one of our cases it was necessary to give the agent 250 days before we could bring the basal metabolic rate to normal. This patient had a large toxic adenomatous goiter and we know that patients with toxic adenomatous goiters require a longer period of preparation to get their metabolic rates to normal than do patients with exophthalmic goiters.

We know that in patients with exophthalmic goiter (primary hyperthyroidism), we can usually bring the metabolism to normal in the number of days that the basal metabolic rate is above normal, and in this group of patients this is quite dependable. In patients with toxic adenomatous goiter about twice the number of days is required to bring the basal metabolism to normal, but there are a good many exceptions to this; it often takes three or four times the number of days that the metabolic rate is above normal to bring it to normal in this type of thyroid toxicity.

One of the problems which bothers us in preparing patients for surgery is the patient who, after prolonged administration of the antithyroid agent, appears clinically well, with weight gain, drop in pulse and so on, but when the metabolic rate is determined the day before operation, it is found to be slightly elevated, as +20 or +28. It is in those cases and in cases of borderline hyperthyroidism that the plan developed by Dr. Elmer C. Bartels in this clinic, and about which we have so often written, has been of great value. He suggested that the metabolic rate be determined under PENTOTHAL® anesthesia. He has demonstrated that the false untrue metabolic rates, such as +25, when done under pentothal anesthesia will be found to be normal, and that truly elevated metabolic rates of +25 or +30, when done under pentothal, remain elevated. This is an extremely valuable method of separating the false from the truly elevated metabolisms.

It would be wrong to promote the use of pentothal during the metabolic test without calling attention to the danger of laryngeal spasm and the necessity for having at hand a competent anesthetist so that, with the larynx cocainized, an endotracheal tube can be introduced should such laryngeal spasms occur. It is not a procedure to be done in one's office or to be done without this precaution. Without this precaution an avoidable fatality could occur.

As we discuss this subject, and relate it to the two girls previously discussed, I note that the girl who has been having propyl thiouracil, whose metabolism came down to +19, has in my opinion been having an inadequate dose of this agent. She has been having 100 mg. of propyl thiouracil daily. That is not enough. She should have a minimum of 200 mg. daily. If she had a toxic adenomatous goiter or severe primary hyperthyroidism with a large thyroid, she should be given 300 mg. and if her metabolic rate does not come down promptly she should have 400 mg. daily.

Our general rule in preparing patients for surgery with propyl thiouracil has been to give 200 mg. per day, 100 in the morning and 100 at night, in cases of primary hyperthyroidism or exophthalmic goiter, and 300 mg. per day, 150 in the morning and 150 at night, in cases of toxic adenomatous goiter.

We have frequently called attention to how undesirable it is to give these patients with hyperthyroidism propyl thiouracil until their metabolic rate has reached minus degrees. The reason for this is that if many thyroidectomies are done on such patients, there will be an increased need for tracheotomies in them. Three things bring this about; perhaps the most important one is that oxygenation of the respiratory centers is diminished in patients with minus metabolic rates, and the second is that patients with minus metabolic rates do not tolerate morphia well and their respiratory centers are further depressed. Furthermore, it is well known that if patients have advanced degrees of myxedema there will be myxedematous infiltration

of their cords, which will narrow the glottic space and reduce cord activity. Everyone who has dealt with hyperthyroidism has known for a long time that two things are true; one is that the patient with severe hyperthyroidism tolerates enormous doses of morphia without respiratory depression, and the other is that the patient with hypothyroidism tolerates small doses badly as relates to respiratory depression.

One of the questions which is frequently asked of me by visitors to the clinic is, what are the various diagnostic measures by which one may definitely establish the diagnosis of hyperthyroidism and in what order do you place their value, such as the basal metabolic rate, blood cholesterol values, blood iodine studies and radioactive iodine uptake?

First let me say a few words about blood iodine studies because we have now had a blood iodine laboratory for a number of years. It has now been possible for some time to fractionate the iodine of the blood accurately into its organic and inorganic components. In patients with hyperthyroidism there is usually an increase in the organic fraction of the iodine as it represents the hormonal fraction; otherwise they would not have true hyperthyroidism.

The difficulties of blood iodine determination for routine diagnoses are time, cost and inaccuracies. It is a time-consuming test, it is an expensive test and it is an extremely delicate test. In addition to that, one must be absolutely sure of certain other factors which are not always easy to obtain from patients who come from distances. The most important one is to know the normal blood iodine for the community from which the patient comes. We know that the normal blood iodine for people from New England is around 8 to 9 micrograms per cent because we are on the seashore, but in Ohio and certain districts along the Great Lakes front, it is considerably lower. One must know also whether or not the patient is taking any medication that contains iodine, and whether or not he has been eating an excess of seafood. All of these "ifs" and "ands" often make the test an extremely delicate one from a scientific point of view and not a very practical one from the clinical point of view.

The uptake of radioactive iodine is an extremely valuable diagnostic test as measured by the Geiger counter, but it too requires special equipment and facilities for the management of these patients, for the disposal of the excretions and for the maintenance of patients within a protected room while it is employed. It is not a test that can be universally used except in centers organized for the employment of this material.

The determination of the blood cholesterol has little or no value in the diagnosis of hyperthyroidism since the ranges in the downward direction which characterize hyperthyroidism are of short excursion. In the upward direction, as for myxedema, the test has real value. It too is a delicate test capable of error except in a well controlled laboratory doing this test frequently.

Basal metabolism remains the best clinical method of confirming the clinical diagnosis of hyperthyroidism and has over the years demonstrated its effectualness and practicality.

I am constantly being asked how I feel about the use of radioactive iodine in the treatment of hyperthyroidism. We probably represent what could be called in this field the opposition, which is always in my opinion valuable. It has been my experience that every time something new like radioactive iodine comes out, there is an excessive wave of enthusiasm for it that carries men far beyond reasonable bounds in the employment of such a new method. It eventually gets back perhaps too far to the other side and then finally comes to its proper level. It will take time for radioactive iodine to find its place, as has been true of the antithyroid agents and many other things in medicine and surgery. At the present time I can only say that my own feeling about radioactive iodine is that in the hands of men who wish to employ it on a limited number of cases in order to demonstrate its effects and who are capable of using it wisely and cautiously and can and do select and follow the cases carefully, it is all right, but its indiscriminate use would, I believe, bring about many unfortunate consequences and do great damage.

There are two things about radioactive iodine that worry me, and if I had a daughter of 16, 18 or 20, I would under no circumstance permit her to be treated with it. One is that radioactive iodine produces thyroiditis, that this will be eventually followed by cicatrization and that I have many times seen recurrent laryngeal nerves run through thyroid tissue. It will take another 10 years or more before it can be determined

whether or not there will be such scarring as to involve nerves or the blood supply of parathyroids following such extensive thyroiditis as results from the destruction of thyroid tissue by the bombardment of thyroid cells from within the acini outward. The other thing that would worry me is that in spite of the fact that biophysicists believe that the dose of radiation used is not large enough to be dangerous to the ovaries, I would still not be certain of the effects of radioactive iodine in terms of mutation changes. This too will take a generation or two to prove whether or not it is a danger to be really feared. Meantime, we have a method proved by past experience, subtotal thyroidectomy, that produces good results with a low mortality and a low morbidity. Our mortality rate in the 2100 patients with hyperthyroidism prepared for surgery with the antithyroid agents has been 0.21 per cent.

THERE is one place where radioactive iodine is of value and that is in the patient who has had multiple inadequate operations for hyperthyroidism with recurrences. Such is the scarring of the inadequately removed thyroid in these cases that the anatomy of the thyroid gland is greatly confused and radioactive iodine here is of real value.

I can only say, as has been said by Dr. Shields Warren who has been interested and active in atomic energy developments and their application to medicine, and who is the head of the Pathological Department at the New England Deaconess Hospital where our pathology is done, that radioactive iodine as the method of treating malignant disease of the thyroid has in our hands been a great disappointment. It has been effective in the group of cases that have done well with radical surgery and irradiation and has been disappointingly ineffective in group 2 and 3 cases of cancer of the thyroid that have not done well with these methods.

While we are discussing some of the problems of hyperthyroidism, it might be well to mention some of the mistakes that can be made in the diagnosis of a patient with an elevated metabolic rate. We must not forget that the metabolism can be elevated by hypertension and that the symptoms of hypertension, with tachycardia, activation and flushing, often closely simulate those of hyperthyroidism. We must also remember that pheochromocytomas during their stage of activity with paroxysmal tachycardia produce a marked increase in the basal metabolic rate which promptly falls as soon as the pheochromocytoma has been removed. We must likewise not forget that the symptoms and appearance during the attacks of paroxysmal tachycardia associated with pheochromocytomas closely simulate those of hyperthyroidism. We have had 8 patients with pheochromocytoma and at least half of these have been sent to this clinic because they had an elevated metabolic rate, periods of activation with tachycardia, sweating, and have been suspected of hyperthyroidism.

Still another thing that must be remembered is that the acromegalic patient maintains an elevated metabolism. We have had a number of patients with acromegaly who have had superimposed hyperthyroidism, and even though we relieved them clinically of their hyperthyroidism, they still maintain elevations of their basal metabolic rate. It is also well to remember that aortic stenosis results in an elevation of metabolism. Even in cases of perforated ear drum, if the perforation is large enough and the eustachian tube open, there can be such escape of fluid that the closed circuit apparatus is no longer in a closed circuit.

I believe that if basal metabolism testing is accurately done, clinically interpreted and well correlated, it is one of the most dependable and practical methods which we have at hand for corroborating the clinical diagnosis of hyperthyroidism.

I have often spoken before medical audiences on the dangers of intractable exophthalmos, and I would like to warn against two or three things in connection with this danger. Intractable exophthalmos often follows subtotal thyroidectomies which have been followed by myxedema, but the important point to which I wish to call attention is that gradually increasing prominence of the eye eventually results in such lid pressure that the cornea is unable to continue its nourishment by means of osmosis. Once this ridging or wrinkling as the result of lid pressure becomes great enough, there will eventually be erosion, infection or ulceration, and then there is danger of slough and the loss of the patient's eye.

Thanks to the work of Dr. Howard Naffziger of San Francisco, these eyes can now be managed by the decompression operation, done through the frontal bone, elevating the frontal

lobe and unroofing the bony orbit. Dr. Horrax, Dr. Poppen and Dr. Freshwater, the neurosurgeons in the clinic, have now operated on 68 of these patients, and of these the eyes were saved in every case. In addition to this it is now possible, by increasing the radicalness of this operation, not only to relieve these patients of the lid pressure which so often results in slough but, in many instances, to permit the eyes to recede so that the unsightliness can be largely overcome.

A very important point in connection with these cases with such distressing and dangerous forward projection of the eyes is that during the period of time that the patients are being sent somewhere to have this operation done every effort should be made to overcome lid pressure, if a competent ophthalmologist is at hand. The lids should be sutured with interrupted mattress sutures of fine black silk, with a gutta-percha strip placed under each loop to prevent the stitches from pulling through, as devised by Dr. James L. Poppen of this clinic.

In closing, I would like to call attention to one thing in relation to a paper on discrete adenomas of the thyroid and the dangers of malignancy, by Dr. Hugh F. Hare and myself, read at the San Francisco meeting of the American Medical Association. At various times we have warned against the danger of malignant degeneration in discrete adenomas of the thyroid but at this meeting Dr. Hare and I reported a consecutive series of 1,971 discrete adenomas of the thyroid in which the incidence of malignancy was 10 per cent. If this incidence is compared with the incidence of malignancy in multiple adenomas, which is 0.61 per cent, it becomes evident that the hazard of malignant disease in the discrete adenomas compared with the multiple colloid adenomatous goiter is very great because the discrete adenoma is a true tumor while in most instances multiple colloid adenomatous goiter is a degenerative process.

We have been a little self-conscious about preaching two or three things in connection with the discrete adenomas of the thyroid. One is that all the discrete adenomas should be removed. With the proof as to the dangers of malignancy reported in these 1,971 cases, we no longer are self-conscious and we believe that every discrete adenoma of the thyroid should be removed. The second thing is that we have been a little self-conscious about taking out small adenomas of the thyroid, the size of one's thumbnail, but if the incidence is 10 per cent, as it definitely has proved to be, then the smaller the adenoma, the better is the reason for taking it out because the longer it is present the greater is the chance for malignancy, and the smaller it is, the easier it is to get it out. The third thing we have been a little self-conscious about has been the removal of discrete adenomas in young people. We no longer feel self-conscious about this, because we have learned that the younger the person with discrete adenoma of the thyroid, the higher the incidence of malignancy.

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DRS. LEVINE AND WIENER TO RECEIVE PASSANO AWARD

Selection of Dr. Philip Levine of the Ortho Research Foundation of Raritan, New Jersey, and Dr. Alexander S. Wiener, Brooklyn, New York, as joint and equal recipients of the Passano Foundation Award for 1951, is announced by the Foundation's Board of Directors.

The work on which the award will be made relates to the discovery and clinical application of the Rh factors in human blood. Presentation of the $5000 cash award will be made at a dinner at the Marlborough-Blenheim Hotel, Atlantic City, on the evening of Wednesday, June 13.

The Passano Foundation, established in 1943 by The Williams & Wilkins Company, Baltimore, Maryland, is dedicated to the encouragement of medical research, especially that having clinical application.

Diagnostic Clinic

The Medical Aspects of Hypertension

WRIGHT R. ADAMS*

UNIVERSITY OF ILLINOIS SCHOOL OF MEDICINE, CHICAGO

This is a presentation of a patient with hypertension, illustrating the transition from the benign to the malignant phase of this disease. Emphasis is placed on the importance of the diastolic pressure, the urine findings and the appearance of the ocular fundi in distinguishing this change.

I SHALL begin by presenting a patient with hypertension. This is a 47-year-old pharmacist whose complaint at the moment is shortness of breath. He is hospitalized at present for this symptom.

He was first told of the presence of hypertension after routine physical examination in 1944. One year previous to this an insurance examiner had not mentioned his blood pressure and had approved him for a policy. No symptoms of hypertension were present at that time, but the patient described himself as nervous, irritable, restless and easily upset by the difficulties of work. I think that perhaps his description was in error in one respect, for he worked in a drug store in a neighborhood which had deteriorated while he worked there, and the business difficulty which upset him most was the fact that his store was held up every week or two because of the presence of narcotics. This business pressure tended to make him irritable and restless. I have some sympathy with him.

There was a questionable history of hypertension in his father.

I saw this patient initially in 1946. At that time he showed the following positive findings: he had no symptoms, but there were slight crossing changes, that is, indentation of the veins by the arteries in the ocular fundi. The heart was slightly enlarged, about 1 cm. beyond the midclavicular line. His blood pressure was 182/126 and the heart rate was 104. This slight tachycardia was, I think, the result of uneasiness at the initial examination and did not persist, as is frequently the case. His blood pressure, both systolic and diastolic, tended to be a little higher when the heart rate was rapid.

The electrocardiogram gave evidence of moderate hypertrophy. Chest x-rays confirmed a clinical finding of slight enlargement of the heart. Intravenous pyelograms were normal and the kidney function was normal as measured by various methods.

He was followed at irregular intervals and had very few complaints until recently. He occasionally had moderate headache but really nothing else. The blood pressure remained at about the height mentioned, around 180/120, until fairly recently. In recent months it has tended to rise, with readings of 200/140 and 260/160.

Hemorrhages in the ocular fundi were first noted in January, 1949. In September, 1950, papilledema and blurring of the optic disks appeared.

For two weeks before his present admission

*Professor and Chairman of the Department of Medicine, University of Chicago School of Medicine, Chicago, Illinois.

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to the hospital he had noticed the onset of an increasing shortness of breath, first on exertion and then on lying down—orthopnea. This progressed rapidly until he was sleeping in a sitting position and requiring aminophylline and morphine for rest.

A severe episode of air hunger and wheezing occurred a few days ago, which brought him into the hospital. At this time physical examination showed that he was anxious, had rapid and labored respirations, the heart rate was 120, the blood pressure 244/150, the skin was moist and warm and the ocular fundi showed small fresh hemorrhages and exudates with marked arterial narrowings and crossing changes. Papilledema was present bilaterally.

There were signs of a small right pleural effusion. Moist râles were heard in both lung bases. The heart was enlarged to 4 cm. outside the midclavicular line in the fifth interspace. The sounds, however, were of good quality. The liver edge was palpable two fingerbreadths below the costal margin.

The urine showed albumin in moderate amounts with occasional hyaline and granular casts and a moderate number of red blood cells. The hemoglobin was 11 gm., red count 3.7 million, and the blood urea nitrogen 122 mg. per cent as compared with the normal limit of 15, which meant that his kidney function was at a very low level and he was in uremia.

Now I propose to review our thinking in handling this man since 1946.

There are five types of etiology for hypertension listed in Table 1, with illustrative diagnoses under each heading. After we study the patient and rule out all except the first group we are still left with between 85 and 90 per cent of hypertensive patients, except for one group that is very hard to quantitate—hypertension as the result of anxiety states. This sort of hypertension, of course, is much more common than that of any other group except essential hypertension, but usually can be readily identified.

TABLE 1

CLINICAL CLASSIFICATION OF HYPERTENSION

1. *Essential hypertension,* benign and malignant.
2. *Renal hypertension,* which results from renal arterio- (or arteriolo-) sclerosis, other arterial lesions, nephritis, pyelitis, amyloidosis, congenital malformation, urinary tract obstruction, etc.
3. *Hypertension of cardiovascular origin,* which results from arteriosclerosis of large arteries, arteriovenous shunts, coarctation of the aorta, etc.
4. *Hypertension of endocrine origin,* such as that associated with hyperthyroidism, acromegaly, pheochromocytoma, Cushing's syndrome, etc.
5. *Hypertension of nervous system origin* as in anxiety states, the diencephalic syndrome, increased intracranial pressure, porphyria, etc.

This man, after appropriate study, fell into the class of essential hypertension, as 85 to 90 per cent of our cases do.

OFTEN the question arises: How vigorously should we study cases to make these diagnoses of occasionally occurring, unusual types of hypertension? Ideally everybody ought to be studied, but quite obviously this isn't practicable for the full-scale study that is required. I should like to suggest that unless clinical methods give a lead as to some unusual type of hypertension I should regard the patient's age as very important. A hypertensive of less than 40 years of age should be studied very vigorously and carefully to find without fail the occasional case which may be helped by some treatment appropriate for an unusual type of hypertension. The patient beyond 60 is usually not so important; he is important to himself, of course; he is an important patient and should be important to the doctor, but the likelihood of one of these unusual types of hypertension is very much less beyond the age of 60. Between 40 and 60 the incidence of unusual types amenable to specific treatment decreases progressively with age.

This man was studied fairly vigorously. However, it became clear that his diagnosis was essential hypertension.

When we have the diagnosis of essential hypertension, I think one of the most important points to make in deciding the outlook for the patient is the differential diagnosis between benign and malignant forms. The etiology of essential hypertension is unknown. Almost certainly it is a catch-all diagnosis with multiple etiologies. I rather suspect that we are at about the same place in the identification of the cause of hypertension, which, after all, is a physiologic reaction and not a disease, as we were 70, 80, 90 years ago in understanding the cause of fever. Then it was very common, and still is to some extent, to treat fever as a symptom without regard to its etiology.

As time has gone on we have been able to

identify the etiologic factors in an increasing number of cases of fever, but occasionally even yet we have to treat the symptom fever, the reaction fever, without understanding the etiology. Currently, so far as hypertension is concerned, we understand the etiology only in a minority of cases, and the so-called essential hypertension includes the great preponderance of cases with high blood pressure, just as the term "cryptogenic fever" identifies a small remaining group of patients with fever where the etiology is not determined. It is almost certain that this group of essential hypertension cases will be whittled down gradually and it will be found that there are multiple causes of the disease.

Perhaps with that "whittling" we will come to understand why so-called benign hypertension exists and why so-called malignant hypertension exists. Some insist that they are two diseases. I think it is much more probable that they are different phases of the same disease. Benign hypertension goes slowly, progresses gradually, and is often compatible with considerable length of life. Malignant hypertension goes rapidly and usually results in a comparatively early death.

It would appear that the major differentiation between the two has to do, in some poorly understood way, with the quality of the walls of the blood vessels, particularly the finer arterioles. In essence, as a general statement, benign hypertension is associated with a narrowed bed, with firm, functionally good vascular walls, whereas malignant hypertension is characterized by a peculiar kind of medial necrosis in the walls of the finer arteries, which is quite different from arteriosclerosis and seems to be a lesion of an entirely separate type.

The differentiation between the benign and malignant phase is of primary importance because of prognosis. I think that a comparatively few simple rules can be given as a basis for diagnosis in this differential aspect, in establishing a differential diagnosis between benign and malignant hypertension. The level of the systolic pressure is practically no good at all; the level of cardiac function or renal function or evidence of vascular accidents in the brain has nothing to do with the differentiation, for all of these functions may deteriorate in the absence of malignant hypertension, and, as you know, the patient may live his life and die from hypertension without ever having entered the so-called malignant phase. However, if he does so his downward course is likely to be slow.

In the malignant phase the diastolic pressure is usually high, and, while there is no arbitrary borderline that is safe, in general people with malignant hypertension have diastolic blood pressure levels above 130 mm. of mercury.

The second point of interest and of value is the urine examination. Damage occurs in the kidneys at a fairly early stage, and the one outstanding finding important above all else in the diagnosis of the malignant phase of hypertension is microscopic hematuria. If there is a considerable number of red blood cells in the urine, the chances of the malignant phase of hypertension being present are very great. There may be, of course, coincidental causes of hematuria, but the hematuria rarely is significant as a result of hypertension in the benign phase.

The third point of differential diagnosis that is of tremendous importance is the examination of eye-grounds. We all hate to use the ophthalmoscope, but it is not very hard to do, and in these cases it is a very rewarding procedure.

Both the benign and the malignant phases of hypertension are accompanied by abnormalities in the retina and the retinal vessels. These deviations from normal are different. The benign phase may show narrowing of the arterioles and indentations of the veins by the arterioles. Often the continuity of the vein is apparently interrupted because the lumen is practically emptied by the high pressure within the arterioles. Normally the arterioles are narrower than the veins but in the presence of hypertension they become even narrower. There may be hemorrhages in the benign phase but usually they are not numerous or widespread. White exudates appear in the retina but these are usually "hard"—that is, they are relatively small and the edges are clearly outlined. The borders of the optic disk are sharply defined.

The malignant phase may show all of the abnormalities seen in the benign phase and some others as well. The hemorrhages are often more numerous and the exudates frequently show fuzzy borders. They are spoken of as "soft." The most characteristic evidence of the malignant phase of hypertension is papilledema. This is characterized by elevation of the optic disk and the loss of the normal clear outline. Swelling of the disk usually submerges the vessels so they are not seen as they traverse the edge.

When first seen in 1946 this patient showed no evidence of the malignant phase. In January, 1949, he had a few hemorrhages in the eye-grounds, but this did not establish the diagnosis of the malignant phase. About eight or ten months ago his blood pressure began to go up—the diastolic pressure before that time had regularly been below 130. Since then it has almost always been above 130 and he has entered the malignant phase of hypertension. The character of the exudates changed and a couple of months ago papilledema developed. His eye-grounds now pretty much resemble the latter picture.

Prognosis is very grave, not because he has gone into heart failure (that is not, of course, a favorable sign but many patients with benign hypertension go into heart failure and can be carried for very many years), but because of the fact that his diastolic pressure is rising, he has microscopic hematuria, and his eye-grounds show papilledema and other evidences of the malignant phase of hypertension. When this particular phase of hypertension is well developed in all these characteristics, a bad prognosis is justified and will almost inevitably be correct. The number of patients reverting from the malignant phase to the benign is very, very small if they occur at all.

On the other hand, the patient with benign hypertension may be in heart failure and may look very bad but the prognosis must always be guarded; if these patients maintain the benign phase, which they may for a long time, they are one of the group who often live to bury the doctor who made the bad prognosis. When patients die in the benign phase they usually die as a result of heart failure. This occurs in somewhat more than half the patients. Renal insufficiency and cerebrovascular accident are less common causes of death.

Having stressed this primary point—the possibility and significance of the differential diagnosis between benign and malignant hypertension—I should like to say a few words about treatment. I shall not dwell upon one of the most important aspects of treatment because you have all heard it discussed and have read about it at great length, but I should just mention the fact that I am convinced that general treatment, modification of the patient's way of life, mild sedation, homely psychiatric treatment (I mean by "homely" the sort of support and effective psychotherapy which any good physician can give) are, all added together, of primary importance and do an enormous amount to lengthen the life of these people.

Among the newer treatments the uses are very limited. Sympathectomy is a brutal procedure which has very limited benefit so far as lengthening life is concerned, in my opinion. Middle-aged people who are in the benign phase I think are better, in almost every instance, not subjected to sympathectomy. Such a high percentage of them live for 20 or 30 years that sympathectomy is not justified.

Probably the ideal place for sympathectomy is in a relatively young person with a fairly labile blood pressure who is showing the beginning signs of the malignant phase of hypertension so that one can be justified in concluding that there is not much to be lost by this brutal procedure and that the situation is a fairly desperate one. Unfortunately, unless you get these people at the very beginning of the change to the malignant phase, sympathectomy is completely useless.

Thiocyanate, which is a very popular drug, I have found to be of limited use. There is no objection to using it as something to try provided the therapy is carefully controlled and there are frequent determinations of the thiocyanate level. This is very important, because thiocyanate is a very toxic drug in overdose. I am a little doubtful whether use of this drug is worth the trouble in most patients. Probably its greatest usefulness is in satisfying a restless patient.

I should like to say just one word in closing about Veratrum viride alkaloids, which are the latest white hope in this disease and which, I am sure, like a great many other white hopes, will turn gradually grayer as months pass. Fortunately, most Veratrum viride alkaloids are relatively inactive and can be used without trouble. I should like to suggest, however, that there is one preparation which should be approached with great care because it is highly effective, and that is the preparation which only last year was accepted by the Pure Food and Drugs Administration, although it has been worked on for some time—VERALOID.® This drug will lower blood pressure. There is only one trouble with it—the amount which it takes to lower blood pressure is very difficult to predict and it often lowers it practically to nothing. It should be used with great caution.

Diagnostic Clinic

Thyroiditis, Simple Goiter and Carcinoma of the Thyroid

GEORGE CRILE, JR.

CLEVELAND CLINIC, CLEVELAND

Subacute thyroiditis appears to be becoming more common, but because of the diversity of the manifestations of this disease it is often unrecognized. Appropriate treatment gives prompt relief of the symptoms. Low grade carcinomas of the thyroid are common in young patients, and all discrete nodules of the thyroid occurring in younger patients should be suspected of being carcinoma and should be removed along with all of the thyroid lobe on the affected side.

THROUGH the courtesy of Dr. Laws and Dr. Cole, this morning we are going to present 2 patients with diseases of the thyroid.

The first patient is 43 years of age and four years ago her physician informed her that she had an adenoma of the thyroid. She had no symptoms from this at the time, but in the last three months, if I am not incorrect—

PATIENT: Six months.

DR. CRILE: —six months, she has noticed a distinct choking sensation. Would you show us what that makes you feel like doing? Clear your throat. She has a feeling that there is something stuck in her throat. This has been going on now for the past six months, and in the last three months she has had some discomfort in the side of her neck, radiating she thinks out to the shoulder. Has that been a sharp pain?

PATIENT: No, it is a feeling of fullness.

DR. CRILE: It has been more a feeling of fullness, she says; no actual pain. Yet on examination she has a distinctly tender neck on the left side. Right there she winces, and there is a little enlargement of the left lobe of the thyroid, which is rather diffuse. It is quite soft; in fact it is difficult to outline.

You also find that for many years you have had a tendency to sigh. Is that correct?

PATIENT: Yes.

DR. CRILE: Thank you.

The question, of course, immediately arises: Why has this adenoma, which we will assume has been present for the past four years, suddenly begun to give this patient difficulty? Why has she a sense of discomfort in the side of her neck, and this choking sensation? But almost more important is the question of whether or not these symptoms are in any way related to the physical finding of the adenoma in the thyroid. She does have, as we have already mentioned, this rather diffuse enlargement of the left lobe. It seems tender, that you cannot deny—it is an objective finding—but the tenderness is not exquisite; it is not such as you see in the ordinary subacute thyroiditis. Furthermore, this has been going on now for six months, which is a little long for the average subacute thyroiditis to last. Also, it is localized to one side of the neck; in six months it has failed to spread from the left lobe to the right, which again would be different from the ordinary common variety of subacute thyroiditis.

It is my clinical impression that this patient's symptoms are mainly functional in origin, that they are due to globus and to a chronic state of nervous tension.

Her manifestations of this tension are in the clearing of her throat, the feeling that some-

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thing is in there—symptoms that are typical of globus. There is no actual dysphagia; she has noticed a little hoarseness at times, but there is no abnormality of the function or appearance of the vocal cords on examination.

The question always arises in these patients as to what to do from the therapeutic standpoint. Are you going to help this patient by removing the thyroid, or are you going to do her harm by further concentrating her mind upon her neck? When she gets too much of a fixation on the neck she will begin to interpret the scar as painful and she will develop many other symptoms. Many times these patients develop various types of hysteria. Even hysterical aphonia may develop after thyroidectomy which is performed with good intentions in patients whose symptoms are not actually due to the thyroid gland or to disease of the thyroid gland itself. The decision as to whether or not the adenoma should be removed is a grave question and, in this particular case, one which I would be unable to decide on a single examination like this.

If I were to see this patient in my office I would attempt to reason with her, to go into the emotional problems of her background, to reassure her, and to carry her along until this particular crisis of anxiety is past. Then if you wish to remove the thyroid at some later date, fine, but it may be that after this matter is completely explained to her the symptoms will subside and nothing will be necessary.

On the other hand, it may be that she will desire that you assure her before operation, which you cannot promise at all, that her symptoms are all going to be relieved by operation. If she still desires operation despite the fact that you cannot promise relief, if she still has a fixation, then under those circumstances I believe it is justifiable to go ahead and remove the thyroid. But the possibility of failure or of the development of new symptoms should be discussed with the patient and recorded in the chart before operation.

GEORGE CRILE, JR.

I WISH to discuss briefly the types of thyroiditis, because thyroiditis today is becoming a common problem. In the first place, some patients who come in with subacute thyroiditis are diagnosed before they arrive as having globus. They are often diagnosed as having fever of unknown origin. Many of them come in with a diagnosis of acute pharyngitis. Some of them have had teeth extracted because of the pain which radiates up to the jaw and to the ear. Some of them have had treatment supposedly directed toward chronic infections of the ear. Some of them have had treatment for menopausal symptoms or for chronic nervous exhaustion. All these mistakes have been made because subacute thyroiditis may simulate a number of totally unrelated conditions.

Subacute thyroiditis we believe is a virus infection of the thyroid. Basically it is a self-limited disease. If you don't treat it at all, it sooner or later goes away, but it may last for a year or even longer. Its course can be tremendously shortened by the use of roentgen therapy in small doses, only 600 to 800 r usually being required to cause a complete subsidence of the process within a matter of a week or two, or possibly as long as a month.

This disease may cause temperatures as high as 104° F.; it may cause exquisite tenderness of the thyroid, or it may cause merely a hard thyroid which is hardly tender at all but is associated with great feelings of prostration and weakness.

Invariably there is a high sedimentation rate; invariably there is practically no uptake of radioactive iodine by the thyroid gland in these

patients in spite of the fact that their symptoms at times may simulate hyperthyroidism. Sometimes they are first diagnosed as having cancer or adenoma of the thyroid, particularly when the disease is limited to one lobe, as it often is in the early stages of the disease. For that reason I wish to call this disease to your attention, to focus your attention upon the fact that it exists. If you feel the thyroid gland itself you will feel that characteristic enlargement and hardness of the lobe—not a very large lobe, maybe almost normal in size, perhaps twice normal, but the firmness and the symmetrical diffuse involvement of the entire lobe or more often of both lobes of the thyroid are the key to the diagnosis, and usually, but not always, the thyroids are tender.

This diagnosis can be confirmed clinically by the high sedimentation rate, the lack of take-up of radioactive iodine, or by therapeutic trial on small amounts of roentgen therapy. If you wish, the diagnosis can be confirmed histologically by the use of the Silverman needle, a biopsy needle with two flanges which can be used in the office to get a good biopsy of thyroiditis and give you definite histologic proof of what you are dealing with. Histologically this disease is the same as the so-called pseudotuberculous, granulomatous or foreign-body type of thyroiditis. It may be very acute or very chronic. We choose to call it subacute.

Riedel's thyroiditis is so rare that you can disregard it for all practical purposes. These patients are considered to have inoperable carcinomas of the thyroid—huge, fixed masses that seem to be totally inoperable; that is the characteristic picture of Riedel's struma.

Struma lymphomatosa is the third type of thyroiditis and seems to be occurring with increasing frequency. It appears to be a diffuse metabolic type of disease. The whole gland is enlarged. Usually it is mistaken for a nodular goiter. The diagnosis can be made on the basis of the diffuse hardness of the thyroid or by the finding of a low basal metabolic rate associated with what appears to be a multinodular goiter.

Sometimes actual myxedema is present. Since a subnormal basal metabolic rate is not common in patients with multinodular goiters its presence should always raise a suspicion of the possibility of struma lymphomatosa.

Under those circumstances the diagnosis can be confirmed by needle biopsy and many of these patients (I won't say all) respond favorably to roentgen therapy, the tumor mass disappearing or becoming very much smaller, and the pressure symptoms abating. About 1800 r usually is required. There is no real need to remove these glands surgically, because they do the patient no harm except from the mechanical symptoms of pressure, and if these can be relieved by roentgen therapy, so much the better.

To leave thyroiditis for a moment and take up an entirely different subject, we have, again through the courtesy of Dr. Laws and Dr. Cole, another patient. This lady is only 20 years of age, and she has a visible lump in the right lobe of her thyroid. This has been present for three years, since she was about 17 or 18, and it has been enlarging recently. It has given her no symptoms whatsoever.

A young woman 20 years of age has no business at all having a solitary tumor of this sort in her thyroid, and any solitary tumor in the thyroid must be viewed with suspicion. That is particularly true when the patient who has this tumor is young. If she were 60 or 70 years of age you wouldn't be too much surprised to see her with a solitary adenoma in the thyroid, because that might just be one involutionary nodule in a multinodular goiter of the type that is so common in people of that age group. In our part of the country, the region of Lake Erie, the incidence of palpable multinodular goiters in people over 50 years of age runs between 5 and 10 per cent of the population at large, and it is rare that you find at autopsy a completely normal thyroid gland without evidence of involutionary nodules.

For these reasons and because involutionary nodules are so common in older people, one can safely disregard, in the older people, any multinodular goiter, or even a solitary nodule if it be very soft and if the patient says it has been there for many years, or if it shows a calcium ring on x-ray, indicating degenerative process in an adenoma. In the older people we don't worry about multinodular goiters so much, but it is in these younger people that we don't like to see the solitary discrete adenoma of the thyroid. I like Dr. Lahey's term "discrete adenoma." It means it is a tumor set apart from the rest of the thyroid, a distinct entity, a true tumor as compared with the involutionary nodules that occur in older people.

This girl has a true tumor of the thyroid. It is

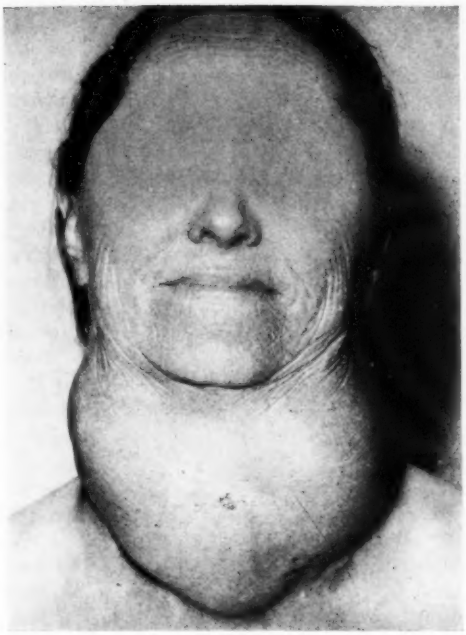


FIGURE 1. Multinodular goiter.

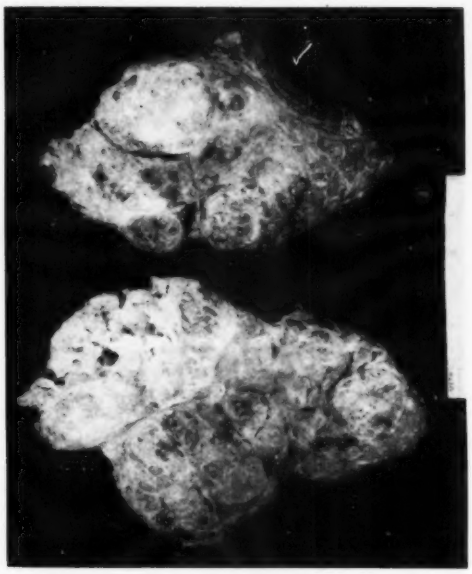


FIGURE 2. Gross appearance of multinodular goiter. The nodules are involutionary rather than neoplastic.

not hard. I don't think it is a cancer. Cancers of the thyroid almost always are hard. Some types of carcinoma may be firm and rubbery but most of them are hard, particularly the papillary carcinomas, which are so common in this younger age group. This feels to me more like a cyst, but her age and the fact that it is enlarging and the fact that it is already large enough to be of cosmetic importance are clear indications not for removal of the adenoma but for removal of that lobe of the thyroid, because if this tumor should happen to be a carcinoma and you have just enucleated the adenoma, you have not cured the carcinoma. If you are going to operate on these patients at all you should perform an operation which will be curative of the carcinoma of the thyroid.

The basic question today is: What types of goiters should be removed? I think it is perfectly apparent to anyone who lives in the Great Lakes area that you cannot do mass removals of all palpable thyroid glands, nor do I think that you would gain anything by so doing. We do not believe that carcinoma of the thyroid occurs very much more commonly, perhaps two or three times as commonly, but not much more so, in the normal thyroid than in the multinodular goiter. Furthermore 80 per cent of the carcinomas of the thyroid which prove to be incurable occur "out of the blue," in patients who never knew, before this highly malignant tumor began to grow with great rapidity, that anything at all was wrong with the thyroid gland. For these reasons I do not consider that the prophylactic removal of nodular goiters does much to prevent development of cancer of the thyroid. Removal of a discrete adenoma, on the other hand, is most important and should be considered not as a prophylactic operation but as a curative operation planned to cure a possible cancer which may be present at that time. For this reason I select for operation those patients in whom I cannot be sure that the tumor in the thyroid is not cancer. If I feel perfectly content that this is not a cancer of the thyroid, it can be disregarded, particularly, as I say, with soft multinodular goiters. A simple enlargement of the thyroid is no indication for a cancer operation.

If you are dealing with a discrete nodule, you have an entirely different proposition and this type of tumor demands a lobectomy.

To illustrate this a little further, I would like to review with you the basic philosophy which

FIGURE 3 *(right)*. Discrete adenoma of the thyroid.

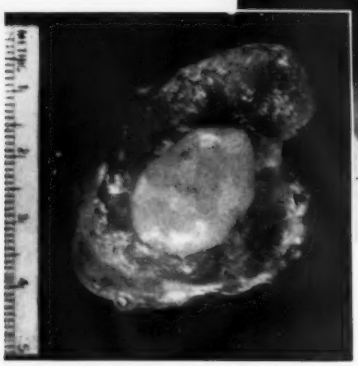


FIGURE 4 *(left)*. Gross appearance of discrete adenoma of the thyroid. This is a true neoplasm.

underlies these remarks. The patient shown in Figure 1 had a typical large endemic goiter, physiologic in its origin, due to goitrogens, iodine deficiency, or whatever reason you wish.

The gross specimen will show multiple nodules, involutionary nodules distributed everywhere throughout the gland (Figure 2). None of her thyroid is normal. That is what I mean when I speak about involutionary nodules. I do not fear the development of cancer in these patients, because cancer of the thyroid, after all, is one of the rarest causes of death from cancer; it stands around seventeenth in the list of fatal cancers of the body. If you were going to remove the thyroid in the 5 to 10 per cent of the older people in this part of the country who have palpable nodules on the thyroid, the mortality might easily exceed the incidence of death from carcinoma. We remove this type of gland because of hyperthyroidism, because of its size, because of pressure symptoms, but not for fear of cancer.

In Figure 3 we have the so-called discrete adenoma of the thyroid. This man has had this tumor for many, many years. This is a true tumor of the thyroid. This is as much a true tumor as is a carcinoma of the breast or a fibroadenoma of the breast. The same thing applies to the thyroid as does to the breast in that if you have multiple nodules throughout the breast you assume that that is more of a pathologic physiology; it is an abnormal endocrine stimulation; you don't worry about the diffuse nodularity of the breast, but if you have a discrete single nodule in an otherwise normal breast you worry about it because it may be a true tumor, a benign one, or a malignant one, and the same is true of the thyroid.

A true tumor of the thyroid, a solitary adenoma in an otherwise normal thyroid gland which may be benign or malignant, is shown in Figure 4. It is impossible to tell by physical examination, or even by examination of the gross specimen, whether it is malignant. This question depends chiefly upon whether or not the veins are invaded microscopically. Eighty per cent of the incurable cancers of the thyroid occur in people who had no previous indication of thyroid disease. These cancers grow with great rapidity, kill in a matter of months, and in our experience are invariably incurable regardless of how early they are treated. This is

the undifferentiated carcinoma of the thyroid, one of the most highly malignant tumors there is, constituting perhaps a third of all malignancies of the thyroid.

The papillary carcinoma is the opposite extreme and occurs characteristically in young people. The average age of the patients that we are operating upon today for papillary carcinomas of the thyroid is now 29 years. This is a disease of youth, of the twenties. The primary tumor may be very small, less than a centimeter in diameter, while the secondary nodules in the lateral cervical region may attain much larger sizes.

If you are willing to sit down and take the time to do a careful dissection of the various groups of nodes which are involved, it is not necessary to cripple these young women and it is not necessary to deform them by performing the usual radical block dissection which is advised for squamous cell carcinoma of the head and neck. It is not necessary because the sternomastoid muscle is not involved by the tumor, and it is not necessary because the result following operations of this type in the hands not only of Dr. Black and Dr. Pemberton at the Mayo Clinic but in our experience at the Cleveland Clinic has been equal to or even better than that reported following radical operation.

Actually, in 26 consecutive cases of papillary carcinoma occurring in young women in whom the primary operation on the thyroid was performed by me, every single one of those 26 patients has remained well now for periods of from 1 to 15 years, averaging 5 years since operation, and none of them today has any evidence of recurrence or metastasis. To be sure, several of them have had several operations, some as many as three operations; quite a few of them have had two, because you may turn up with contralateral metastasis or a tumor outside the field of the first operation. But the important thing is that all are well and none are mutilated. This is a different type of tumor from most cancers that you think of, and a very slow-growing, almost benign type of tumor.

No radiation therapy need be given. One patient even had axillary metastasis and bilateral cervical metastasis. She has remained well for two years following operation. That is too short a period of time for a follow-up of this type of case, but it is probably significant nevertheless.

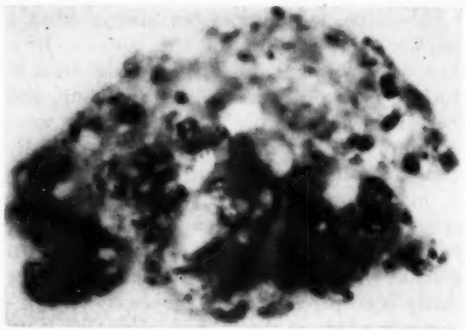


FIGURE 5. Radio-autograph showing irregular distribution of I^{131} in multinodular goiters. Papillary carcinomas, when they take up I^{131}, also tend to take it up irregularly.

One patient has had a papillary carcinoma of the thyroid, proved by biopsy, for 28 years. Twenty-eight years ago Dr. T. E. Jones removed one of these nodes which you can barely see in her lateral cervical region. She has subsequently refused all forms of therapy; she has had no radiation, no operation, and yet you can see that the tumors are barely visible. These are metastatic papillary carcinomas of the thyroid. These patients go on for many years. Just last week we treated with radioactive iodine a patient whose primary tumor had been removed 20 years before and whose chest was completely filled with marble-sized growths. This patient has now been under treatment with radioactive iodine for about six months, and the metastases have disappeared under radioactive iodine therapy. I do not claim that we have helped this woman much because she had lived 20 years with pulmonary metastases and they caused her no symptoms. Even if we had not treated her at all with radioactive iodine she might very well have lived another 20 years in perfect comfort. I point this out to you merely to indicate that these tumors are remarkably slow-growing and benign in their course.

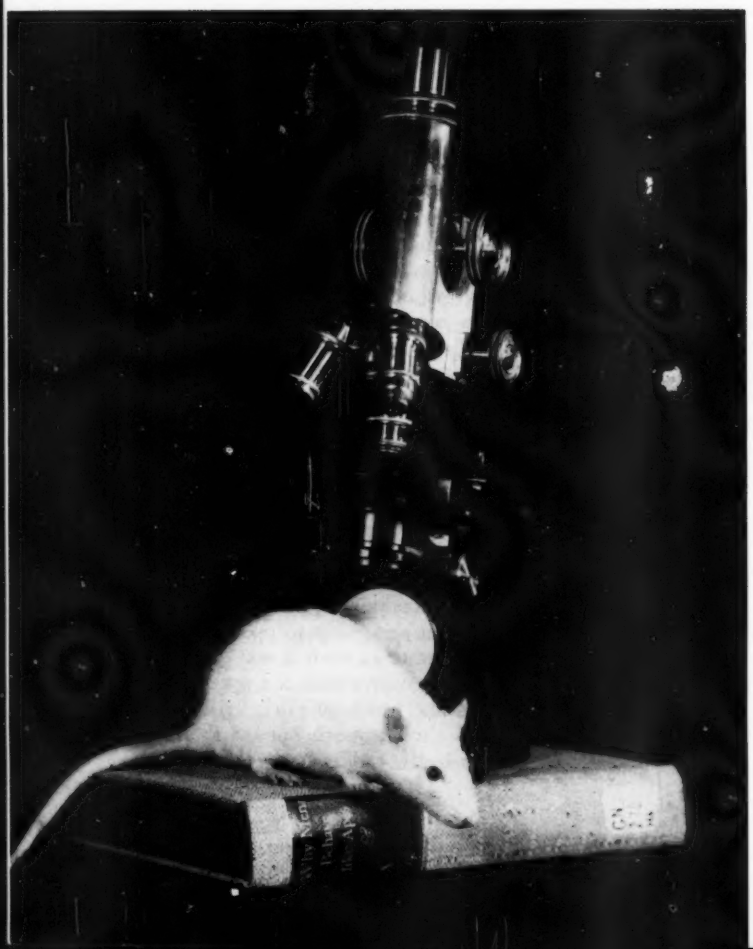
The results of incomplete operations may be disastrous and may result in incurable local recurrences of tumors of low malignancy. These tumors can implant themselves in the neck following incomplete operations, and so again it is important, if you are going to operate upon them at all, to operate in such a way that the entire lobe and the entire tumor are removed.

Radioactive iodine has been effective in controlling many of these tumors, but for the reason that you see in the radio-autograph (Figure

5) radioactive iodine does not always effect a complete disappearance of the tumors. It is taken up too irregularly. There are the areas in which a great deal of iodine is taken up, and others in which hardly any is, and so some areas are knocked out and others aren't. By repeated small doses of 30 or 40 millicuries you can many times completely knock out these tumors and control them, but it takes a long time and the ultimate results will not be known for many years. All we can say is that we see a fairly high percentage of remissions and primary regressions in the patients who take it up satisfactorily.

I believe that the most important factor in control of cancer of the thyroid is the operation that is done for a discrete tumor of the thyroid. This operation should include ligation of the inferior thyroid artery, identification and preservation of the recurrent laryngeal nerve, and removal of the entire lobe.

In summary, therefore, of this controversial subject of carcinoma of the thyroid and its treatment, I think that it is fair to say that the first decision the surgeon has to make is whether he is dealing with a true neoplasm or merely with an involutionary nodule. Once that decision is made the indications are clear. Certainly you would remove the sizable goiters regardless of their nature, but I am speaking now about the question of cancer only. If the patient has a soft multinodular goiter, barely palpable and not of cosmetic importance, disregard it; the chances of cancer are much too little to make any difference. If, on the other hand, it is the solid discrete type of tumor, then don't operate to prevent cancer but operate to cure cancer and do a proper initial operation.



"ART AND SCIENCE"

(Photograph by Jack Davidson. Reproduced courtesy of *Popular Photography*.)

Diagnostic Clinic

Causes and Treatment of Menopausal Bleeding

JOHN I. BREWER*

NORTHWESTERN UNIVERSITY MEDICAL SCHOOL, CHICAGO

Efforts to establish the cause of the climacteric bleeding must be made by complete physical examination, smear, biopsy and curettage. Five to 17 per cent of such patients have pelvic malignancies and are treated accordingly. For the remainder curettage is adequate to relieve the symptom in some but the majority are best treated by vaginal hysterectomy.

MENOPAUSAL bleeding is a symptom of such great importance that we believe a special classification of patients should be made.

The term "menopausal" or preferably "climacteric" bleeding should be defined. First, by bleeding we mean abnormal uterine bleeding—excessive, prolonged or cycles too frequent—or spotting, or continuous bleeding. We would like to emphasize the fact that any bleeding different from that to which a particular patient is accustomed should be considered as abnormal in a patient in the climacteric age. The term, "climacteric age," has come to mean that period at the termination of her menstrual life during which a woman undergoes certain physiologic changes. There is no definite point of beginning of the climacteric, nor is there a direct and absolute termination, so certain beginning points and end points must be made arbitrarily.

We have selected the age of 45 as the relative time of beginning of the climacteric, and we have taken one year after the last menstrual period as the time at which the climacteric is over. Now, we know that is only relatively true, and for purposes of definition and of management of patients with climacteric bleeding, those points are relatively accurate. Any bleeding that occurs one year or more after the cessation of the last menstrual period is considered postmenopausal bleeding.

Malignancy is by far the most important entity that is associated with abnormal bleeding; from 5 to 17 per cent of women who have abnormal bleeding during the climacteric have malignancy of the genitalia. Any such symptom which is accompanied by such a high incidence of malignancy requires that we treat the patient with special care. If one includes women who have postmenopausal bleeding, you can readily see the increase in the number of patients who will have malignancy if they have abnormal bleeding.

One climacteric patient is mentioned here because she had only a slight increase in menstrual flow and yet had a cervical cancer. In the past, some of the most famous specialists in this country have stated that excessive bleeding or slight prolongation of bleeding at menstrual time in women in this age group was of no significance, that those patients did not need

*Professor of Obstetrics and Gynecology, Northwestern University Medical School, Chicago, Illinois.

Presented at the thirty-fifth annual Assembly of the Interstate Postgraduate Medical Association, Chicago, 1950.

investigation nor did they require treatment, and one said, "Never is bleeding of this type indicative of or present with carcinoma." Well, that is a completely erroneous statement, and this particular patient well exemplifies it. We still maintain that any abnormal bleeding, however minimal, must be investigated.

I mention these investigative procedures and technics because a great deal is written about their value. I list them only, because for practical purposes we do not use them. We rely on the simple things that are available to all without any special training. We like to do our gynecology in a practical and simple way, and while we do these tests on occasion, we do not advocate their use in any routine manner. They do have certain values, but we believe you can practice excellent gynecology without their employment.

One of the first things that I should like to mention about the investigation is that it is absolutely impossible, visually or by palpation, to diagnose early carcinoma of the cervix. The examination of patients must go far beyond the clinical examination. For example, I had a patient who had an apparently normal cervix. She had had children and the cervix was lacerated, but there was no evidence of a lesion in that cervix, nor did the patient have any symptoms. Yet there was a carcinoma in the cervix.

I do not wish to go into the argument of what represents early invasion in carcinoma of the cervix, nor to argue about carcinoma in situ or preclinical carcinoma. I only wish to say that carcinoma in its early stages can be present in a cervix which is entirely normal both to inspection and to palpation. It is present before symptoms are produced. A patient may have cancer in the cervix, as you all know, for many, many years before it becomes evident. We have one patient who in 1931 had a cervical biopsy which consisted of a wedge excision of the cervix. Examination of the microscopic sections showed only a cervicitis. In 1949, we were doing routine Papanicolaou smears. The patient was asymptomatic; the smear was positive for cancer. A biopsy was positive for cancer. We went back to the block of tissue and the sections of 1931. The sections showed only cervicitis. We took the block of tissue, cut it in two, reimbedded it in paraffin, made a section from the center of that block of tissue, and found there had been carcinoma in 1931. In other words, for 18 years carcinoma had been present in the cervix without symptoms. That is not at all unusual.

One does not need to use Papanicolaou smears; one can use biopsies instead, but when you use both, the percentage of correct diagnoses will improve.

We never treat a patient on the basis of a smear alone. A positive smear was obtained on one patient but the biopsy showed a perfectly normal squamous epithelium. Because of the smear we turned this little biopsy tissue over and sectioned the other side, which we wouldn't have done if the smear had not been positive in this asymptomatic patient.

The other side of the biopsy showed carcinoma. This lesion would have been missed with a biopsy alone; it was picked up by a smear, and the smear made us persist in searching for the cancer until we found it. Errors can be made in smears, in biopsies and in gross examinations. If all are done together you may accomplish more than by any one or two of the methods together.

Often one fails to investigate patients with climacteric bleeding because the patient has been curetted six months or a year before. We maintain that you must repeat the investigation and you must repeat it at intervals. We have a rule in the management of climacteric bleeding that you may investigate once, and you may do it a second time, but at the second time you must also treat the patient.

Failure to investigate may be because the patient is receiving estrogens. In spite of the fact that patients are taking estrogens, it must not be forgotten that bleeding can occur from carcinoma while the patient is receiving estrogens. We simply stop the estrogens; if bleeding continues for over three weeks we assume that the bleeding is due to a specific lesion and not to the endocrine therapy.

In our personal experience, about one third of the patients with climacteric bleeding had only diagnostic studies which consisted of smears, biopsies, and dilatation and curettage. Of course, all general diseases are excluded prior to operative investigation. All but a few of the patients were adequately cared for by this simple procedure, there being no recurrence of the bleeding during their follow-up period.

Approximately two thirds of the patients had definitive treatment. All of these had some

lesion or combination of lesions for which we believed therapy was indicated. To mention a few, one of the most common was polyps. In the management of cervical polyps, our usual procedure is to remove the polyp in the office, put it in fixing solution for microscopic section, and at the same time we do a Papanicolaou smear. Prior to the time of the smear and our routine use of it, we hospitalized all patients with polyps for curettage because on several occasions we removed the polyp only and then found the bleeding to be coming from a higher lesion—carcinoma of the endometrium or endocervix. We now rely on the Papanicolaou smear to a certain extent and hospitalize less of these patients.

We have set up certain rules for hospitalization: we hospitalize the patient if it seems improbable that the bleeding is from the polyp, if the bleeding is continuous or continues after polypectomy, if the smear, biopsy or polyp suggests malignancy, if there is some dilatation of the cervix necessary for stricture of the cervix, if the pedicle is large, if the polyp is large, or if the polyps recur.

The patients with fibroids and bleeding during the climacteric were treated by hysterectomy in most instances. Carcinoma of the cervix is treated by radium (4000-5000 mg. hrs.) followed by roentgen therapy (7000-9000 roentgen units, measured in air).

We prefer preliminary radium therapy (2500 mg. hrs.) in the management of cancer of the endometrium. This is followed in approximately four weeks by a complete abdominal hysterectomy and bilateral salpingo-oophorectomy. In most cases, roentgen therapy is also given.

Endometriosis with coexisting abnormal uterine bleeding in climacteric women is treated surgically. While the uterus is removed in such instances, the ovaries are not routinely removed in the patient who is 45 to 50 years of age. Definite indication for their removal must be present. Each patient with endometriosis must be individualized and decisions concerning the tissues to be removed are not made until the organs and lesions are carefully examined at operation.

Functional bleeding in women of this age group is best managed by curettage and if this does not relieve the symptom, a vaginal hysterectomy is performed. Hormonal therapy is not utilized.

Lacerations of the childbirth canal and uterine descensus that require correction are best managed by repair and vaginal hysterectomy in women of this age group if abnormal bleeding is present and if the bleeding is not the result of a pelvic malignancy.

As you can see, we believe that hysterectomy has a foremost place in the management of abnormal bleeding in climacteric women. It was performed in about two thirds of the patients who were admitted to the hospital for this symptom. Less radical curettement will relieve the symptom in approximately one third of patients. It is stressed that a diagnosis must be made before hysterectomy is performed. We rarely employ the Manchester procedure and never use the Watkins interposition operation in climacteric women with bleeding.

This brings us to what we think should be indications for hysterectomy. There has been considerable argument and a great deal of discussion and criticism of hysterectomy. I know some of you will not agree with certain indications for hysterectomy which we use, but they seem logical to us in climacteric bleeding.

These indications are: abnormal bleeding after a previous dilatation and curettage (that means, of course, in climacteric women); profuse or persistent bleeding, even though we find nothing (if the woman is having continued bleeding we believe at that age hysterectomy is the procedure of choice). Often an adenomyosis will be found which cannot be diagnosed prior to surgery. Another thing is the presence of persistent atypical cells in the vaginal smear, cells that cannot be called cancer—we cannot locate a cancer, and yet the atypical cells persist. In women of that age we believe sacrifice of the uterus is indicated. If the woman has relaxation plus bleeding, prolapse of the uterus plus bleeding, uncontrollable anemia, or a large uterus which may contain adenomyosis with bleeding, vaginal hysterectomies are done in practically all cases.

Other indications for hysterectomy are severe dysmenorrhea plus bleeding, coexisting pelvic pain the cause of which cannot be found, and concern of the patient over malignancy. Some patients are so disturbed about malignancy that they will not be reassured and as a result they are emotionally disturbed to such an extent that for them hysterectomy may be a procedure of

choice. That is put last and is the weakest point that I have.

For specific treatment, then, we feel curettage after a smear and biopsy will relieve approximately a third of climacteric patients with abnormal bleeding. The remainder are preferably treated by hysterectomy, and in our own clinic preferably by vaginal hysterectomy. We do not use radium or roentgen therapy in the treatment of abnormal uterine bleeding in the climacteric, nor do we use irradiation of any type in the treatment of benign pelvic lesions. This was discontinued by us in 1939. We reserve irradiation for the treatment of malignancies.

So much for menopausal or climacteric bleeding. I would also like to mention postmenopausal bleeding. The incidence of cancer is tremendously high in women who have bleeding after the menopause (60 per cent). These patients must all be investigated without exception. Our feeling also is this: that a woman who has postmenopausal bleeding may be investigated once and by choice should be treated at the same time; second, that if you so desire, she may be investigated once without definitive treatment, but should bleeding continue the investigation must be repeated and this time we feel it is absolutely necessary that treatment be instituted.

When you curet a postmenopausal woman you may be disturbed by the pathologist's report of endometrial hyperplasia. The relation of endometrial hyperplasia to carcinoma is not scientifically or accurately described. That hyperplasia is a precursor of carcinoma is by no means certain, in spite of some evidence to the contrary. When one finds endometrial hyperplasia in a postmenopausal uterus something has made the hyperplasia; some stimulation has been present. There are those—particularly in Sweden there is one investigator—who say that any woman who has a postmenopausal hyperplasia must have her abdomen opened and have the tubes, uterus and ovaries removed, because in 90 per cent of cases she will have some tumor in the ovary. To this we do not subscribe. There may be a stromal hyperplasia of the ovarian tissue which produces enough estrogen, postmenopausally, to stimulate the endometrium. However more often than either of these two things (tumor or stromal hyperplasia of the ovary) nothing at all is found to account for the hyperplasia.

In postmenopausal patients, as well as in climacteric women, irradiation is not used in the management of benign lesions. Hysterectomy or some lesser surgical procedure, if such is indicated, is the procedure of choice. Irradiation is employed if there are definite contraindications to hysterectomy or if malignancies exist.

"Quite frankly, Mrs. Johnson, your anxiety neurosis has me worried."

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Pathology in General Surgery*

Postgraduate Medicine *is pleased to offer a selection of reproductions and excerpts of the descriptive text from "Pathology in General Surgery," in this and the June issue. As a representative sampling of the nearly 400 outstanding color plates of gross and microscopic features of each clinical entity, together with the comprehensive presentations of each disease, these reproductions and discussions indicate the wealth of valuable material contained in Dr. Schafer's book.*

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Embolus in Right Pulmonary Artery

Plate 59.—Snakelike, dark-red, clot, 20 cm. long, found coiled in the bifurcation of the right pulmonary artery at post mortem examination of a fifty-nine-year-old man, who died suddenly on the fourth day following left total pneumonectomy for carcinoma of the left bronchus.

*Pathology in General Surgery. By Paul W. Schafer, M.D., Professor of Surgery and Chairman of the Department, University of Kansas School of Medicine. 581 pages, with 495 illustrations, 368 in color. 1950, The University of Chicago Press, Chicago. $17.50.

THROMBO-EMBOLIC DISEASE

Peripheral vein thrombosis is a subject of major concern in surgery. In this connection most writers make a sharp distinction between phlebothrombosis, that is, thrombosis occurring in the absence of inflammation of the vein wall, and thrombophlebitis, which results from and is associated with a frank inflammation of the vein wall. Both conditions are seen under similar circumstances, being particularly common in persons who are confined to bed, as occurs following operation. The exact cause for the condition is not known, but sluggish venous blood flow and trauma to veins are important factors, and these are brought about by decreased muscular activity in the lower extremities, compression of veins of the thigh and calf during operation and in forced maintenance of the horizontal supine position postoperatively, abdominal distention, impairment of both diaphragmatic and intercostal respiratory motions, etc.

The thrombosis may be first detected clinically on examination of the calf, where it will be found that the patient complains of tenderness on direct palpation along the course of the deep veins, whereas compression of the overlying muscle, fat and skin is nonpainful. Later dorsiflexion of the foot will produce pain in the calf (Homan's sign).

Later yet the patient may experience pain either in the calf or in the medial aspect of the thigh as he attempts to move his leg, and by this time there is usually edema and cyanosis of the foot and of the lower leg.

Following most operations the patient presents a normal pulse, temperature, and respiratory rate by the third or fourth day. Persistent elevations, otherwise unexplained, may be accounted for on the basis of such a thrombosis. More commonly the patient's postoperative course is entirely uneventful for 7-10 days, and then a small, sharp spike in the TPR curve will be noted. Examination at this time will usually reveal the presence of a deep venous thrombosis of the lower extremity, though the patient may have had no complaint referable to this area.

At times a pulmonary embolus causing pain in the chest, dyspnea and cyanosis will be the first warning of the presence of a peripheral venous thrombus. The embolus may be small, in which event infarction of only a small area of the lung will result. Most distressing is the occurrence of a massive pulmonary embolus causing sudden death. The unexpected suddenness of this major catastrophe makes even worse its utter finality. Typically the patient is without postoperative complaint and, on getting out of bed for the first time or while coughing, straining at stool or urination, suddenly experiences severe pain in the chest and exhibits marked apprehension, cyanosis and dyspnea. Death usually supervenes in from a few minutes to one or two hours.

At postmortem examination the pulmonary artery will be found occluded by a solid, snakelike red or mixed thrombus, which when removed is found to be a perfect cast of the common iliac, femoral and popliteal veins or portions thereof, often bearing on its surface markings indicating the location of valves in these vessels. The right pulmonary artery is in most direct line with the pulmonary conus and is thus the most common site for lodgment of such emboli, particularly in its branch to the right lower lobe of the lung. Large emboli may straddle the pulmonary bifurcation ("saddle embolus"). At times the embolus is smaller, and one may wonder as to the cause for sudden death. This usually is explained on the basis of a severe reflex vagotonia with its resultant effect on the bronchi, coronary arteries and the heart itself.

Though pulmonary embolism may complicate both phlebothrombosis and thrombophlebitis, it is well known that the massive fatal form is most prone to occur in the former condition. In frank thrombophlebitis the thrombus is likely to be more firmly adherent to the vein wall, and those emboli that do form are usually of small size and represent fractured proximal fragments of the thrombus. In phlebothrombosis, where little adherence exists, the major portion of the thrombus may be dislodged.

The presence of a thrombophlebitis with local vessel tenderness and edema and redness of the overlying skin of one extremity does not necessarily mean that a pulmonary embolus occurring in such a case arose from the obviously involved extremity; indeed, it more likely had its origin in an unsuspected phlebothrombosis of the opposite, apparently uninvolved extremity. The emboli which arise from thrombophlebitis of the pelvic veins in women and of the prostatic plexus of men usually do not give rise to massive pulmonary involvement. Thrombi which do not become dislodged eventually are organized by ingrowth of capillaries and connective tissue from the vein wall. Endothelium ultimately covers the thrombus in its unattached areas, and it may become canalized through preferential channel selection via the reparative capillaries or the vasa vasorum. Usually a considerable collateral circulation develops in the region of such a thrombus.

Though pulmonary embolectomy may be carried out under special circumstances, treatment of this condition is largely prophylactic and consists of avoidance, in so far as possible, of those routines which are known to cause injury to the deep veins of the extremities and to impair venous circulation. Prophylactic venous ligation is becoming increasingly popular, as are DICUMAROL® and heparin therapy. The last few years have seen the development of an extensive literature on these subjects, references to which are listed in the book.

Cholesterolosis of the Gall-Bladder

Plate 451.—Numerous plaquelike deposits of cholesterol in the mucosa of a gall-bladder which contains many pure cholesterol stones. The appearance of the mucosa in cholesterolosis accounts for the use of the term "strawberry gall-bladder" to describe this condition.

CHOLESTEROLOSIS

Cholesterol may be deposited in the mucosa of a gallbladder which is otherwise normal, though this change is most commonly seen in association with cholecystitis. Ordinarily the cholesterol deposits appear as discrete plaques located on the apices of mucosal folds. Such plaques are irregular in outline and vary from one to a few millimeters in diameter. They present an opaque yellow color; when viewed in contrast with the reddish background of the gallbladder mucosa, they appear not unlike the seeds of a ripe strawberry. Because of this resemblance the term "strawberry gallbladder" has been applied to this condition. Occasionally an area of mucosa becomes so heavily laden with cholesterol that it projects into the lumen of the gallbladder as a discrete villus, maintaining only a tenuous connection with the remainder of the mucosa. Such masses may break loose to float free in the gallbladder bile, where they have been incriminated as possible nidi for subsequent formation of complex gallstones.

More commonly cholesterolosis is associated with the precipitation of cholesterol crystals from the gallbladder bile with the formation of multiple, small, pure cholesterol stones. Such stones are characteristically of uniform size, varying from one to a few millimeters in diameter. Because of their nodular appearance, each stone seems to represent the fusion of three or more small spheroidal masses of cholesterol.

Uncomplicated cholesterolosis does not produce clinical signs or symptoms, these being referable to associated cholecystitis and cholelithiasis. Small cholesterol stones, because of their size, are particularly prone to cause recurrent attacks of biliary colic. Since they are often present in gallbladders without substantial evidence of cholecystitis, they usually can be visualized by cholecystography.

Microscopically, the cholesterol may be confined within the epithelial cells of the mucosa, but, more commonly, large accumlations are observed in the underlying connective tissue. Large droplets may lie free within the stroma, but more often the lipid is contained within macrophages, or "foam cells"; these may be demonstrated in sections stained with hematoxylin and eosin; however, the tissue presents a more spectacular microscopic appearance when the cholesterol deposits are stained either red with Scharlach R or black with osmic acid. This condition is not to be confused with the foreign-body reaction which is commonly observed about cholesterol crystals.

PLATE 252.—This small benign gastric ulcer was resected because of uncontrollable hemorrhage. A clot is discernible in the floor of the crater. This thirty-seven-year-old man had experienced several previous hemorrhages but in these instances had responded to medical management.

PLATE 253.—In this section the bleeding point is seen in the lower right corner of the crater, where a medium-sized, partially thrombosed artery in the sclerotic ulcer bed has been eroded.

BENIGN GASTRIC ULCER

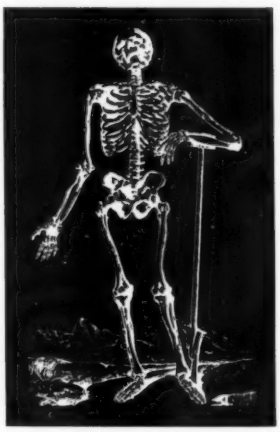
GASTRIC ulcers are seen at all ages, though the chronic benign variety is usually a problem of early to middle adult life. Men are affected many times more often than are women. The disease is probably equally as common as duodenal ulcer, though the anatomic relations of the latter more consistently result in symptoms directing attention toward it. Characteristically the patient with this disease complains of burning or gnawing epigastric distress which appears one to two hours after meals and is promptly relieved by the ingestion of food or alkali. Nausea and vomiting are present only when the ulcer is located near the pylorus, producing cicatricial or edematous obstruction of the stomach, or when the condition is complicated by a reflex cardiospasm. Many times a period of marked nervous tension antedates the onset of symptoms. In from 5 to 20 per cent of patients massive gastric hemorrhage or symptoms and signs referable to a complicating perforation occur without prior clinical evidence of the existence of an ulcer. Typically the fasting gastric secretion and that obtained by histamine stimulation is highly acid. Probably even more significant is the almost constant presence of overnight secretion by the stomach of large volumes of acid juice, a liter or more often being obtained in the 12-hour night resting period.

Much has been written concerning the etiology of this disease. Neurogenic, toxic, dietary, endocrine, infectious, circulatory, traumatic, and other factors have been emphasized by students of this problem. Inescapable in a consideration of etiology is the important role played by the gastric juice itself. Dragstedt has shown that pure gastric juice can digest any living tissue. The regular occurrence of this phenomenon in the stomach is prevented by the protective action of mucus secreted by the gastric glands, as well as by the protective action of ingested food and products of gastric digestion. Furthermore, substantial volumes of gastric juice are normally secreted only at times when food is contained within the stomach, small volumes being formed normally during the resting phase. This contrasts sharply with the large volume of fasting secretion encountered in the ulcer patient.

In the past, emphasis has been placed on those factors which presumably predispose an area of the gastric wall to the lytic action of gastric juice. Infarction, ischemia due to vasospasm or persistent muscle contraction, focal infection of the gastric wall, mucosal abrasion by coarse food particles, and other factors have been incriminated in this connection and are undoubtedly occasionally of importance. However, a substantial mass of experimental and clinical data has now accumulated, suggesting that the overproduction of lytic gastric juice may alone be responsible for the majority of ulcers. The exaggerated secretion which follows the subcutaneous implantation of histamine in beeswax has been demonstrated by Wangensteen to result regularly in chronic ulcer formation.

Although chronic benign gastric ulcers may occur in any part of the stomach, more than 90 per cent are encountered on or near the lesser curvature in its non-acid-secreting distal half. A benign ulcer is occasionally found in the pyloric canal or at the cardia, though a mucosal discontinuity in these areas should always be suspected of malignancy.

The usual chronic benign ulcer is solitary. Typically it is located on the posterior surface of the antrum near the lesser curvature. It varies from a few millimeters to several centimeters in diameter and grossly appears as a sharply punched-out, deep crater with an indurated floor covered by a gray membrane. The ulcer is usually round, though it may be ovoid, its long axis lying at right angles to the line of the lesser curvature. Occasionally marked irregularity in outline is observed. Because of edema and hyperemia, the mucosal margins of the crater may be prominent, though usually they are flat and inconspicuous, contrasting sharply with the nodular marginal protuberances often seen in ulcerating gastric carcinoma. Cicatricial contracture at the ulcer site may produce radiating folds of gastric mucosa. In rare cases scarring may be so marked as to produce a constriction of the stomach referred to as an "hourglass" deformity. Characteristically the side walls of the crater are either precipitous or slightly terraced, though slight undermining, particularly of the proximal margin, may be observed. An eroded artery can usually be demonstrated in the floor of a bleeding ulcer, though its small size is usually surprising in view of the massive hemorrhage which has occurred.



Case Report

Paget's Disease of the Skull Simulating Malignant Neoplasm

ALFRED VOGL* AND HARRY D. FEIN**

NEW YORK UNIVERSITY COLLEGE OF MEDICINE, NEW YORK

Most cases of Paget's disease of the skull can be diagnosed without difficulty. The characteristic x-ray features such as the thickening of the vault of the cranium; the condensed inner table and the blurred, ill-defined outer table; the blotchy and spongy appearance of the affected bones, rightly likened to fluffy cotton-wool; and, in many instances, the basilar invagination as evidence of softening of the base of the skull present a picture that cannot be confused with any other disorder.[1] This classical appearance of Paget's disease of the skull representing the common, predominantly osteosclerotic type may occasionally coexist with the rarer type characterized by extensive demineralization. This latter condition was originally described as a separate entity under the name of *osteoporosis circumscripta*[2] but is now generally recognized as the early, osteolytic phase of Paget's disease.[3] It manifests itself roentgenologically by the presence of a few, usually large, areas of uniform decalcification with sharply defined, wavy outlines, spreading without regard to suture lines.

If these two phases of the disease are seen simultaneously, the resulting x-ray picture may give rise to diagnostic difficulties, particularly in those rare instances in which the osteolytic process has produced numerous small "cystic" defects in the flat bones.[4]

Such a case will be described.

CASE REPORT

H. T., a 66-year-old Negro male, was admitted to the psychiatric medical service of Bellevue Hospital on August 3, 1949. According to his relatives, he had been ill for three years with weakness of the right leg, general muscular stiffness, trembling, thick speech and progressive loss of memory. More recently he had developed urinary incontinence, emotional outbursts and mental confusion. The patient was physically well preserved but showed marked intellectual impairment, with euphoria and poor memory.

Examination of the head disclosed nothing remarkable except for tympanitic resonance elicited on percussion of the frontal bones.[5] The only other abnormal findings included irregular, unequal and completely rigid pupils; spasticity of all the extremities; slight ataxia on the right; hyperactive deep tendon reflexes; ankle clonus and a Babinski response on the left side. The examination of heart, lungs and abdomen was negative.

Laboratory findings were within the range of normal. These studies included urinalysis, complete blood count, sedimentation rate, blood sugar, nonprotein nitrogen, acid phosphatase (2.0 units), serum calcium (9.5 mg. per 100 cc.) and phosphorus (3.09 to 3.43 mg. per 100 cc.). Alkaline phosphatase, however, was elevated to 7.0, 8.4, 8.6 and 8.6 units on four occasions (normal: 1.5 to 4.0 units). Plasma proteins were 6.9 gm. per 100 cc. with an albumin-globulin ratio of 3.8/3.1. Bence-Jones proteinuria was absent on four occasions.

A lumbar puncture was performed with negative results except for an elevation of total proteins to 70 mg. per 100 cc. Spinal fluid and serum serology were negative.

In the course of the workup for the neurologic disorder, an x-ray examination of the skull was performed (Figure 1). It was described as showing numerous circumscribed, sharply outlined areas of decalcification from 3 to 12 mm. in diameter, without sclerotic rims. The clinoid processes were almost invisible. The cranium appeared thickened throughout. The rest of the skeleton including the bony thorax, long bones, pelvis and spine was normal.

The neurologic findings and mental deterioration

From the Third Medical Division (N. Y. U. College of Medicine), Bellevue Hospital, New York.

*Assistant Professor of Clinical Medicine, New York University College of Medicine.

**Assistant Professor of Clinical Medicine, New York University College of Medicine.

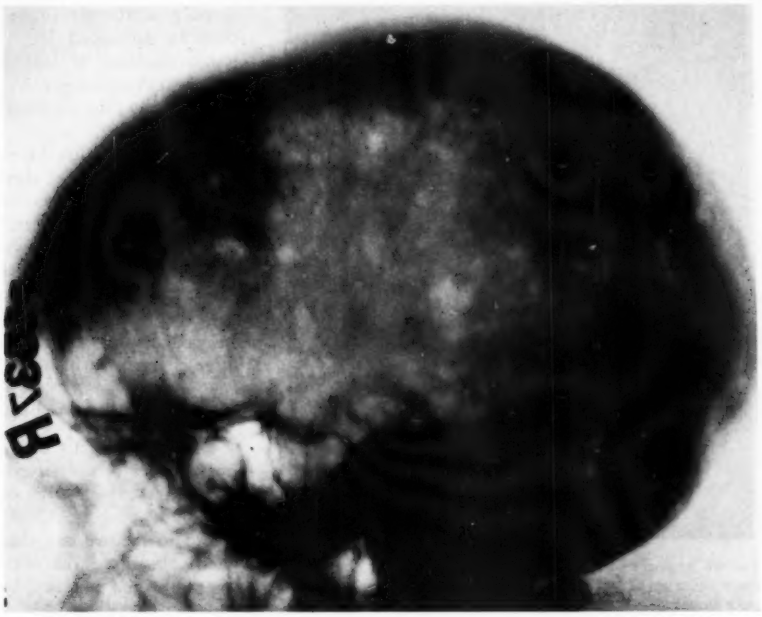


FIGURE 1. X-ray of skull for preliminary examination.

were ascribed to "diffuse cerebrospinal disease, etiology unknown, probably of a degenerative nature."

The skull lesions were interpreted by most observers as due to multiple myeloma or osteolytic metastatic carcinoma. There were, however, several features which were inconsistent with these diagnoses: (1) the considerable thickening of the entire vault (reaching 21 mm. at the vertex and the occipital tuberosity) with marked condensation of the inner table and irregular thinning and blurring of the outer table; (2) the presence of several irregular areas of patchy osteosclerosis (Figure 2) and finally (3) the presence of a clear area (about 20 by 25 mm. in size) of uniform demineralization with an irregular wavy border, adjacent to the frontal sinus (typical of "osteoporosis circumscripta"). All these findings favored the diagnosis of Paget's osteitis fibrosa of the skull. Under these circumstances, we felt that the scattered small destructive bone lesions also represented a phase of Paget's disease, namely the stage of erratic absorption of old bone and formation of noncalcified osteoid tissue.

The tympanitic note found on percussion of the patient's skull tended to support the impression of Paget's disease.[5]

Biopsies taken from two different areas of the parietal bones confirmed the diagnosis. The pathologic report read as follows: Broad, bony trabeculae with typical mosaic arrangement of the laminae. Considerable osteoplastic and osteoclastic activity around the bony trabeculae. The marrow spaces are fibrotic with few large mononuclear cells. No tumor tissue. Diagnosis: Paget's disease.

An extensive search of the gastrointestinal and genitourinary tracts for a possible primary malignant disease revealed no such lesion.

During the four months of hospital stay the patient's condition remained unchanged. Repeated skull films showed an identical picture.

DISCUSSION

THE pathogenesis of osteitis deformans, as established by more recent investigations, is one of gradual remodeling of the affected bone.[4] The process begins with lacunar *absorption* of osseous tissue by osteoclastic activity,[6,7] accompanied by greatly increased vascularity.[8] The next stage is the deposition of large amounts of *osteoid tissue,* which leads to condensation of the bony structure and increase of its width. Finally *ossification* takes place in the newly formed matrix but some of the osteoid tissue may remain uncalcified and even undergo degeneration. All these processes may take place in succession or simultaneously in varied portions of the diseased bone.

While the roentgenologic picture of the "remodeled" and thickened bones with irregular osteosclerosis (producing dense, blotchy shadows in the flat bones) is fairly common, and readily recognized as characteristic of Paget's disease, and while large areas of demineralization of the cranium characterize the atypical or monophasic manifestation of the disease ("osteoporosis circumscripta"), the concomitant occurrence of these two phases is less common and may easily be misinterpreted. Actually, many rather inconspicuous specks of increased transparency can be seen between the

FIGURE 2. Inconsistent with the diagnosis was the presence of several irregular areas of patchy osteosclerosis.

densely scattered, fuzzy islands of osteosclerosis even in advanced Paget's disease. On the other hand, mottling of the translucent fields of osteoporosis circumscripta by the irregular deposition of lime salts into the osteoid tissues can be expected sooner or later.

Decalcification in the form of multiple small and widely scattered foci during the osteolytic process of Paget's disease is definitely uncommon and can easily be confused with the bone destruction of disseminated hematogenous metastases of a malignant neoplasm or by multiple myeloma. Close examination of the roentgenologic picture will, however, virtually always disclose some evidence of the second, productive phase of Paget's disease. The latter changes furnish the clue to correct diagnosis.

SUMMARY

A case of Paget's disease is presented in which the presence of numerous small foci of decalcification suggested destruction by a widely scattered malignant process. Other features of the roentgenologic picture are discussed, the evaluation of which permitted the correct diagnosis. The latter was confirmed by bone biopsy.

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FIRST WOMEN DOCTORS REPORT FOR ARMY DUTY

(Official Defense Department Photo)

Major Theresa T. Woo being greeted by Major General Raymond W. Bliss, surgeon general, as she and Major Ruth E. Church reported in Washington, D. C. They were the first women physicians to volunteer and be accepted for service with the Army Medical Corps since the end of World War II.

Case Report

Intravenous Aureomycin in Acute Disseminated Herpes Simplex

J. MURRAY RIDDELL, JR.,* FREDERICK C. LENDRUM** AND MELVIN M. CHERTACK**

UNIVERSITY OF ILLINOIS COLLEGE OF MEDICINE, CHICAGO

Acute disseminated herpes simplex is a systemic disease with alarming severity, and even at times with a fatal outcome. The cutaneous manifestations are of the greatest diagnostic importance. The older name, "Kaposi's varicelliform eruption," however, is unfortunate. This long established and forbidding term is interpreted by most physicians to mean that the ailment is simply an obscure skin disease. The paradoxical result has been that only the dermatologists have generally recognized that the serious aspect of this ailment is systemic rather than cosmetic.

The commonest history is that of a patient with chronic allergic eczema who develops an apparently benign herpes simplex. After a few days this spreads explosively over the eczematous areas with severe but self-limited constitutional symptoms. Extensive reviews in the dermatologic literature make a detailed discussion unnecessary in the present case report.

Reports on the value of aureomycin in disseminated herpes simplex (Kaposi's varicelliform eruption) have already appeared[1-3] in medical literature. In all except one instance, however, other chemotherapy or antibiotics were also administered so that the specific effect of aureomycin has been difficult to evaluate. In the present case aureomycin, administered intravenously as the sole therapeutic agent, was dramatically successful. Constitutional manifestations were rapidly controlled and the vesicopustules characteristic of the disease had subsided within three days after treatment was started.

*Department of Dermatology, University of Illinois College of Medicine, Chicago, Illinois.

**Department of Medicine, University of Illinois College of Medicine, Chicago, Illinois.

REPORT OF CASE

G. B., an 18-year-old male, had been under treatment for one year in the Eczema Clinic of the Department of Dermatology, University of Illinois College of Medicine, with the diagnosis of atopic dermatitis. On September 20, 1949, "cold sores" developed on his upper lip and chin, and five days later a spreading eruption appeared on the face and neck. Examination on September 29 revealed numerous vesicopustules, some with central umbilication, scattered over the forehead, neck and sides of the face (Figure 1). The cervical lymph nodes were enlarged and tender. There were typical healing crusted lesions of herpes simplex on the upper lip and chin. The patient appeared severely ill, with malaise, fatigue and mild fever. The clinical diagnosis was Kaposi's varicelliform eruption. A biopsy specimen revealed a histologic picture consistent with this diagnosis. Inclusion bodies resembling those seen in herpes were noted in the nuclei of epidermal cells.

Administration of aureomycin was started as soon as the patient entered the hospital. The dose was 100 mg. dissolved in 25 cc. of physiologic saline solution given intravenously at six-hour intervals. Constitutional manifestations subsided within the first 24 hours, and by the third day only small, reddish-brown crusts remained at the site of the vesicles and vesicopustules. The patient was discharged on the sixth hospital day (Figure 2).

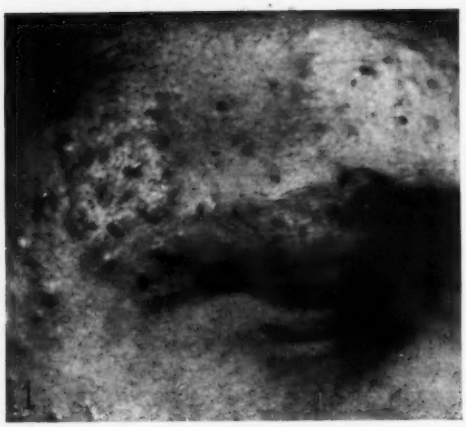

FIGURE 1. Appearance of the lesions around the right eye before therapy.

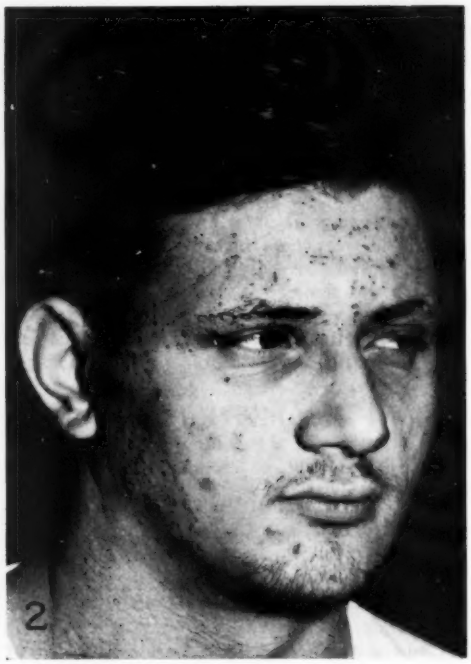

FIGURE 2. Appearance of the lesions after therapy.

SUMMARY

A patient with disseminated herpes simplex (Kaposi's varicelliform eruption), of five days' duration, was successfully treated with aureomycin alone. The aureomycin was given intravenously, 100 mg. every six hours, for a total of 1200 mg. There was remarkable regression of constitutional symptoms in 24 hours and involution of the cutaneous lesions in 72 hours.

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COMING MEETINGS AND POSTGRADUATE COURSES

Roffey Park Institute of Occupational Health and Social Medicine, Horsham, Sussex, England

Two international summer schools on social services in Great Britain, July 30 to August 11; August 13 to August 25. These resident schools are planned for doctors, social workers, psychologists and senior nursing administrators. Case demonstrations, excursions and films have been planned for both sessions. Visitors will be housed in residential country house, 35 miles from London. Attendance is limited to 25. Fee, including full board, tuition and excursions, is £20 ($60.00). Further information and application forms are available from T. M. Ling, M.D., Director, Roffey Park Institute of Occupational Health and Social Medicine, Horsham, Sussex, England.

Oak Ridge Institute of Nuclear Studies, Oak Ridge, Tennessee

Course in the theory and technics of autoradiography, beginning July 2 and continuing for three to four weeks, under the direction of George A. Boyd. Course intended for professional research workers who have completed basic radioisotope technics course given by the Institute or who have equivalent experience in use of radioisotopes in medical or biologic research. Further information and application forms will be available at a later date from Ralph T. Overman, Special Training Division, Oak Ridge Institute of Nuclear Studies, P. O. Box 117, Oak Ridge, Tennessee.

American Physicians Art Association

Fourteenth art exhibition to be held during the A.M.A. convention at Atlantic City, June 11-15. Any physician in the United States, Canada and Hawaii desiring to participate should communicate with F. H. Redewill, M.D., Secretary, American Physicians Art Association, 760 Market Street, San Francisco 2, California.

Mount Sinai Hospital, Miami Beach, Florida

First annual medical seminar in cardiovascular diseases at The Sorrento Hotel, May 23, 24 and 25. Visiting lecturers will include Drs. David L. Abramson and Otto Saphir, Michael Reese Hospital, Chicago; Claude S. Beck, Western Reserve University; Samuel Bellet and Seymour S. Kety, University of Pennsylvania; John W. Gofman, University of California, and Charles W. Robertson, Massachusetts Memorial Hospitals. Registrations are limited to 200 physicians. Fee is $20 for practicing physicians and $7 for interns and residents. Further information may be obtained from: Chairman, Seminar Committee, Mount Sinai Hospital, 4300 Alton Road, Miami Beach, Florida.

GENERAL PRACTICE *Review*

To provide the general practitioner as well as the specialist with concise, readily available information on the latest, proved methods of treatment of conditions commonly encountered in an average practice, POSTGRADUATE MEDICINE *offers this department to its readers. It is not, of course, intended to present these discussions as the only acceptable therapeutic procedures to be used, but rather to offer simple regimens and recommendations based on the extensive experience of the physicians who prepared these summaries.*

Treatment of Herpes Zoster

MICHAEL H. EBERT*

RUSH MEDICAL COLLEGE OF THE UNIVERSITY OF ILLINOIS, CHICAGO

The treatment of herpes zoster is directed toward: (1) inhibition of the virus; (2) healing of the skin lesions; (3) amelioration or relief of the neuralgic pain in the area supplied by the affected sensory ganglion. The pain frequently precedes the skin lesions, usually accompanies them, and occasionally persists for months or years, especially in the debilitated or aged; (4) prevention of sequelae in ophthalmic zoster and (5) treatment of associated paralyses.

INHIBITION OF THE VIRUS

The chemotherapy of virus infections is a very recent development. Aureomycin, when given early enough and in large enough dosage, gives promise in halting the progress of the infection and preventing or diminishing the associated neuralgia. Finland and his associates[1] recommended 1 gm. four times a day for two to four days followed by 0.5 gm. four times a day for three to five days more. The smaller dosage may be used throughout if the tolerance is low. Binder and Stubbs[2] gave 0.5 gm. every six hours for two days with dramatic results in 3 cases and moderate results in 1. Nausea and diarrhea are not uncommon side effects. The expense of aureomycin must also be considered. It would seem that aureomycin should be administered in every case of ophthalmic zoster as early as possible. In other types it is a matter of choice.

*Clinical Professor and Chairman of the Department of Dermatology, Rush Medical College of the University of Illinois; Attending Dermatologist to the Presbyterian and Cook County Hospitals, Chicago, Illinois.

HEALING OF SKIN LESIONS

While the patient's attention is fixed on the skin lesions and he interprets them as the cause of the neuralgia, the physician must remember that the fundamental pathology is in the sensory ganglion. The skin lesions usually heal readily even though they may be hemorrhagic or necrotic. In mild cases the application of calamine lotion N.F. is sufficient. In severe cases aureomycin ointment or a 3 per cent VIOFORM cream is the best application. Since there is hyperesthesia of the area, protection from trauma and changes in temperature is important, especially in elderly patients. A thick layer of sterile cotton under a gauze pad supported by a binder is adequate protection.

AMELIORATION OR RELIEF OF NEURALGIC PAIN

Fundamentally, the hyperesthesia and neuralgia in zoster are due to inflammation or its sequelae in the sensory ganglion supplying the affected skin

segment. Early in the course the edema, hemorrhage and exudate compress the sensory nerves, causing pain referred to their terminals in the skin. Later, the contraction of scar tissue may have the same effect. Findley and Patzer[3] explained the pain as due to local vasospasm and increased vasoconstrictive tone in the vessels of the skin, which is mediated through the sympathetic ganglion by impulses from the cells of the intermediolateral columns of the cord, which are receiving an excessive number of impulses from the irritated sensory ganglion. They blocked this reflex in 4 cases by infiltration of the appropriate sympathetic ganglion with procaine solution. They expressed doubt as to the applicability of this method in trigeminal zoster.

It is difficult on the theory of local vasospasm to account for the favorable results reported by Combes and his associates[4] in the use of dihydroergotamine-45. One cubic centimeter was administered intramuscularly every 24 hours until pain was relieved. At times the dosage was increased up to 2 or 3 cc. There were few side effects. As might be expected, neuralgia of long duration responded poorly to this method. It is possible that the efficacy may be due to the blocking effect on sympathetic impulses although the drug is a vasoconstrictor.

Rosnak[5] infiltrated the affected sensory ganglion as well as the appropriate prevertebral sympathetic ganglion with 0.5 per cent procaine. In ophthalmic zoster only the gasserian ganglion was infiltrated. He stated that the procedure is not without risk and should be attempted only in exceptionally painful cases and only by a competent neurosurgeon or neurologist. Furthermore, the method is not uniformly successful.

Even such radical measures as surgical resection of the dorsal nerve roots running from the ganglion to the cord or the destruction of the dorsal ganglion by alcohol injection may fail to relieve the pain in severe cases.

NONSPECIFIC MEASURES FOR RELIEF OF PAIN

Autohemotherapy—Poth,[6] in a large series of cases, injected 20 to 30 cc. of whole blood drawn from the cubital vein into the gluteal muscles every three days, with excellent results.

Convalescent blood—Becker[7] administered 450 cc. of convalescent blood in 3 cases of ophthalmic zoster and 200 cc. of convalescent plasma in 1 case, with excellent results. The ever present danger of transmitting homologous serum hepatitis should be kept in mind if this method is used.

Surgical pituitrin—The subcutaneous daily administration of 1 cc. of surgical pituitrin has been frequently used with satisfactory results.

Sodium iodide—The intravenous injection of 2 gm. of sodium iodide in 10 cc. of sterile distilled water daily for three days, and every other day for three or four more days, seems to have some value.

Moccasin venom—Dennie and associates[8] administered Lederle's moccasin venom in a dilution of 1:3000 intradermally every two to four days, with marked relief from pain.

X-rays—Foerster[9] recommended filtered x-rays over the involved spinal ganglion, 150 r filtered through 3 mm. of aluminum. This may be repeated once in three weeks.

In order to evaluate properly the various methods used for the relief of pain, it is important to distinguish between (a) the pain associated with the acute phase and (b) the severe persistent postzoster neuralgia. In the early phase sedation with acetylsalicylic acid, phenobarbital or codeine will usually give sufficient relief. Type b, persistent postzoster neuralgia, can be a major problem in therapy. Grinker and Bucy[10] state that the failure, in many such cases, of sympathetic block or sympathectomy, as well as the failure of resection of the affected nerves proximal to the ganglion or destruction of the ganglion itself by alcohol injection, would indicate that the pain is due to a central irritative process, either in the posterior gray columns of the cord or the central medullary nuclei. In any series of reported cases large enough to be of statistical value, treated by any of the methods mentioned, there are a few recalcitrant cases. These are usually of the type b, with neuralgia of long duration.

OPHTHALMIC ZOSTER

Ophthalmic zoster is potentially so serious that the advice of an ophthalmologist should be sought in an attempt to prevent sequelae that might interfere with vision. As already stated, aureomycin by mouth should be started at once and aureomycin ophthalmic solution used in the eye.

POST-ZOSTER PARALYSES

Involvement of the oculomotor nerves with lid-lag, diplopia, etc., may occur in ophthalmic zoster. Bell's palsy is common in zoster of the geniculate ganglion. These paralyses usually heal spontaneously. There is no adequate treatment for the motor paralyses of the muscles of the trunk or extremities that occasionally occur in zoster. Fortunately, they are rare and usually heal without any residuum.

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Management of the Patient in Status Asthmaticus

MAURICE S. SEGAL* AND J. AARON HERSCHFUS**

TUFTS COLLEGE MEDICAL SCHOOL, BOSTON

The proper management of the very sick asthmatic patient can tax the character and therapeutic ingenuity of the physician. The patient generally presents a serious picture of marked physiologic imbalance. Severe hypoxia, cyanosis, dehydration, peripheral vascular shock and drug intoxication may all be present. Death may come suddenly from any of the latter factors, but more commonly it is due to asphyxia resulting from the plugged and obliterated bronchi and bronchioles.[2] The therapeutic problem may be made even more difficult for the physician by the attitude of the anxious, wornout family and the disturbed emotional makeup of the patient.[3]

SEGAL

This discussion will be limited to several phases in the management of the patient in status asthmaticus, and will include the following: (1) water-saline-glucose and aminophylline infusions; (2) the use of epinephrine; (3) the therapeutic use of gases and aerosols; (4) bronchial evacuation—"catharsis" and (5) remissive therapy with the use of pituitary adrenocorticotropic hormone (ACTH).

*Clinical Professor of Medicine, Tufts College Medical School; Director, Department of Inhalational Therapy, Boston City Hospital, Boston, Massachusetts.

**Research Fellow in Medicine, Tufts College Medical School; Resident in Medicine, Department of Inhalational Therapy, Boston City Hospital, Boston, Massachusetts.

WATER-SALINE-GLUCOSE AND AMINOPHYLLINE INFUSIONS

No fixed rules can be established for the composition of the so-called "intravenous cocktail." One may give 5 per cent glucose in saline for the first liter and 5 per cent glucose in distilled water for the second and third liters. Occasionally one may observe a mild relaxing effect from the substitution of a liter of 5 per cent alcohol in 5 per cent glucose during the evening hours. The 3 liters may be given in 24 hours by employing a flow of approximately 30 drops per minute. The judicious use of a salt-free diet, distilled water in place of saline and daily use of 2 cc. intramuscularly of one of the mercurial diuretics may be of great value where the possibility of underlying heart disease or cor pulmonale presents itself. Distilled water should be substituted for the saline in patients who are receiving ACTH.

HERSCHFUS

Aminophylline (theophylline ethylenediamine) in varying dosage may be added to the intravenous infusion.[4] One may begin by adding 0.5 gm. of aminophylline per liter of solution. The dose may then be adjusted downward or upward to 1 gm. per liter of solution, depending upon the patient's ability to tolerate the drug.

How long should one continue to use intravenous infusions? We have continued them for as long as 10 days. If improvement follows one or two days of continuous therapy, infusions may then be given intermittently, e.g., from 9:00 A.M. to 9:00 P.M. daily, reducing the total intake to 1500 cc. Supplementary aminophylline, if necessary, may be given in the form of a 20 cc. intravenous solution containing 0.25 or 0.50 gm. of aminophylline. This should be administered slowly at a rate not exceeding 2 cc. per minute.

The continuous or interrupted infusions may be omitted with evidence of complete freedom from severe paroxysms of coughing or bronchospasm. In their place, aminophylline should then be administered rectally in doses of 5 to 10 gr. in 15 cc. of tap water every 8 or 12 hours. This therapy, in gradually diminishing dosage, should be continued for at least one month after complete recovery.

USE OF EPINEPHRINE

Epinephrine has been employed in various modifications and concentrations and routes. No true idiosyncrasy (allergy) to epinephrine has been reported. However, toxic reactions, intolerance and fastness may occur. These effects are more commonly observed with overdosage and with repeated parenteral use. Deaths have been reported following intravenous administration or an accidental intravenous injection. Caution should be stressed concerning the possibility of reactions from the accidental injection of 1:100 epinephrine and other concentrated sympathomimetic amines which are intended purely for aerosol use.

In general, epinephrine parenterally is limited in its value for the relief of the acute attack. Unfortunately, few physicians or patients limit the dosage to the proper and effective subcutaneous injection of 0.2 to 0.3 cc. of 1:1000 dilution. Generally, larger doses at frequent intervals are resorted to, especially when self administered. The epinephrine-fast state is encountered most commonly in these patients. We have not observed any striking value from combinations of epinephrine 1:500 in various oil and gelatin vehicles employed for a slow release.

Most patients in status asthmaticus are epinephrine-fast, and the repeated use of all epinephrine preparations should be avoided until epinephrine sensitivity is restored. We have made a rule of never adding epinephrine to the "intravenous cocktail." There is evidence that epinephrine invokes the release or production of histamine. Repeated injections may no longer produce bronchial relaxation, but rather manifestations of histamine effect—namely, flushing, headache, tachycardia and bronchoconstriction.

Antihistaminic preparations given intravenously may serve as histamine antagonists or epinephrine sparers in the epinephrine-resistive patient.[5,6] Intravenous BENADRYL hydrochloride or PYRIBENZAMINE hydrochloride may be of value in such instances. Doses of 20 to 50 mg. (10 mg. per cc. of solution) at four- to eight-hour intervals may be administered and continued for one to four days. The antihistaminics should be injected directly into the rubber tubing close to the intravenous needle and not into the infusion fluid. With intravenous benadryl hydrochloride a more relaxed feeling and a short period of sleep may follow each injection. Relief from mild paroxysms of asthma may also be noted.[6] Frequently, following these injections, epinephrine sensitivity to the subcutaneous or aerosol route may be restored.

USE OF THERAPEUTIC GASES AND AEROSOLS

The type of gas mixture used will depend upon the factor responsible for the dyspnea, whether hypoxia or respiratory obstruction.[1,3] If hypoxia is the main factor, oxygen in adequate concentrations, employing equipment most suitable for the patient, should be administered.[7,8] We prefer the use of an oxygen tent with a transparent canopy enclosing the entire bed.[1] The freedom of motion and the uninhibited feeling of being able to see all that goes on is well appreciated by the sick patient. The type of tent which employs electrical refrigeration affords more adequate air-conditioning, humidity control and ventilation without direct drafts on the patient's face. It is simple to operate and eliminates the need for ice and skilled personnel. Oxygen concentrations of about 60 per cent may be maintained. It is our general custom to place the patient in the tent immediately upon arrival at the hospital, and he should remain there until recurrent attacks of severe bronchospasm have subsided.

If obstructive phenomena predominate, mixtures of 75 per cent helium and 25 per cent oxygen are more beneficial than oxygen alone.[7,8] It may be observed that positive pressure inhalation of oxygen or helium and oxygen will clear up signs of pulmonary edema and relieve subjective dyspnea promptly. The patient can be treated in the positive pressure hood apparatus or with the O.E.M. positive pressure mask for one hour, 3 or 4 times daily.[1,3,7,8]

Inhalation of nebulized sprays of various therapeutic agents (VAPONEFRIN, ISUPREL, NEOSYNEPHRINE, penicillin, streptomycin, and water vapor) may be employed for the relief of the troublesome cough, as an aid to expectoration, for relief of bronchospasm and for control of infection.[1,3] Aerosols of vaponefrin or isuprel 1:200 are of particular value for the relaxation of bronchospasm.[9] The combination of 0.5 cc. of vaponefrin or isuprel 1:200 and 0.5 cc. of 1 per cent neosynephrine is of

particular value when there is bronchospasm, accompanied by sticky, tenacious sputum or a troublesome, unproductive cough. Continuous flows of oxygen or helium-oxygen may be employed to nebulize 0.5 to 1 cc. of these solutions several times daily. The vaponefrin nebulizer (small particle size) may be introduced through a vent opening in the tent or hood and placed in the patient's mouth or it may be attached directly to the mask apparatus.

BRONCHIAL EVACUATION—"CATHARSIS"

Bronchial catharsis may be accomplished in a variety of ways. The expectorant drugs (e.g., iodides) are excellent bronchial evacuants. In the very sick patient 1 to 2 gm. of sodium iodide may be added to each liter of infusion fluid and continued for several days. When effective, productive coughing occurs, the iodides may be given orally again. We have also found ipecac of considerable value.[4] Ipecac acts by substituting effective retching in the place of ineffective coughing. Syrup of ipecac may be administered in 2 or 3 teaspoonful doses followed by a cup of lukewarm boiled water. This dose may be repeated several days later, if indicated. It is always worth a trial before attempting bronchoscopy.

Bronchoscopy is a very valuable diagnostic and therapeutic procedure and is indicated whenever a harsh, useless cough with dammed up secretions is present and bronchospasm persists despite adequate physiologic management. Thick tenacious sputum may be removed, large amounts of thinner secretions aspirated, and bronchial drainage facilitated.

One of the most common and important causes of death in asthma is obstruction of the larger and smaller air passages by inspissation of tenacious secretions. At times spectacular improvement may follow bronchoscopic aspiration even in a moribund patient. Because of the danger of serious reactions to the use of PONTOCAINE or cocaine sprays and instillations for local anesthesia in asthmatic subjects, we generally prefer deep surgical anesthesia with ether. Intensive bronchoscopic aspiration is followed by marked subjective and objective improvement. It may prevent atelectatic complications, may prove life-saving and may be followed by a long period of remission.

REMISSIVE THERAPY WITH THE USE OF PITUITARY ADRENOCORTICOTROPIC HORMONE (ACTH)

Several encouraging reports have appeared in the literature describing the use of ACTH and cortisone in the asthmatic patient.[1,10-13] The goal of all therapy in the patient with serious bronchial asthma is the production of a prolonged remission. Frequently, when such a remission occurs, one is unable to explain its genesis. Just as often one cannot bring about a second remissive episode employing the same procedures. ACTH apparently offers a way to cause such a remission more consistently than any other therapeutic regimen we have employed.[14,15]

We have treated a total of 25 seriously ill asthmatic patients with ACTH.[14,15] In this series there were 10 males and 15 females, between the ages of 15 and 73 years. The asthma was of less than five years' duration in 11 patients and of more than five years' duration in 14 cases, with a range of one to 30 years. A total of 34 courses was given; 3 patients had two, and another 3 had three courses of ACTH. Most patients were treated according to the following dosage schedule: 40 mg. initially and repeated in six hours, followed by 20 mg. every six hours until striking benefit had been observed for two days. The time interval was then prolonged to every eight hours for one to two days, or longer if improvement did not continue. Usually after the fourth day of therapy, the time interval was further increased to every 12 hours until the time of discharge. The total dose of a single course varied from 240 mg to 900 mg. and the duration of a course of therapy from two and one-half days through 19 days.

Because of the severity of their asthma, all of the patients received supportive therapy for one or more days, concomitant with ACTH. Many of the patients at discharge, although enjoying a complete remission, were placed on daily supportive medication such as saturated potassium iodide, rectal aminophylline and oral antihistaminics in an attempt to prolong the remissive period.

Physiologic side effects from ACTH never necessitated discontinuance of the treatment in our patients. Mooning of the face, edema, mild euphoria, increased appetite and abdominal distention were observed. Few toxic reactions were seen. Generalized urticaria and mild attacks of bronchospasm were observed in 2 patients, but did not recur with repeated injections. A macular, erythematous nonpruritic rash over the lower extremities was seen in 1 patient; the rash disappeared while treatment was continued. One patient had two nearly fatal anaphylactoid reactions, occurring immediately after injections of ACTH (same lots). Diabetes and hypertension were present in several of the patients, but were not aggravated by the ACTH.

The observed results were as follows:[13-15]

1. Immediate therapeutic effect—(maximum response to treatment regardless of duration)—Failure in 2; fair in 4; good in 4; excellent in 24.

2. Continued therapeutic effect—Failure (less than one week) in 3; fair (one to two weeks)

in 8; good (two to four weeks) in 11; excellent (longer than one month) in seven courses. Five patients have just completed a course of therapy with excellent immediate therapeutic effects. The continued therapeutic effects are being observed.

3. Concomitant improvement of the following disorders were also observed in the patients: rheumatoid arthritis (2 patients); atopic eczema (food) in 1 patient; severe aureomycin dermatitis (1 patient); nasal polyps (3 patients) and seasonal hay fever (2 patients).

Unfortunately the period of remission was generally short. Repeated intensive courses of therapy were more effective than attempts at maintenance therapy. However, repeat courses of therapy should not be employed too freely, inasmuch as the nature of the repeated remissions may not be free of hazard. For the present, the drug should be reserved for the seriously ill (hospitalized) patient, when physiologically directed therapy has failed.

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Ambulatory Treatment of Indolent Ulcer

FRANCIS RAFOOL

PEORIA, ILLINOIS

Economic factors make ambulatory treatment of indolent ulcers very desirable. Many of the patients seen have suffered the pain and work loss of such pathology from one month to several years. All of them have used varied treatments, prescribed by physicians and otherwise. The treatments they had prescribed for themselves in most cases aggravated the local area and caused loss of time for special preparatory procedures.

RAFOOL

Etiology of cases seen—1. Varicose vein stasis with local abrasion—the commonest cause.

2. Sclerosing solution burn, secondary to varicose vein injection, in cases where the sclerosing solution was injected into the tissue rather than the vein. This is more apt to happen in the lower one third of the leg which has less subcutaneous fat.

3. Diabetes mellitus with abrasion.

4. Third degree burns with circulatory deficiency. One case treated previously by Turch graft with some areas failing to take.

5. Pressure ulcers, secondary to prosthesis, and articles of clothing improperly fitted.

Pathology—All of these cases have a common underlying pathology of stagnation of circulation at the locale of the ulcer. This is due to dilation of veins, spasms and thrombosis of arterioles, local release of histamine, excess of carbon dioxide and anoxia, plus secondary infection. Any attempt to heal these ulcers must correct the underlying pathology step by step. Some success has been

achieved by following a procedure like the one to be described, which allows the patient to be ambulant and in gainful labor during the entire treatment.

PROCEDURE

When first seen, the patient is given a complete physical examination including Kahn test, urinalysis, and Perthe's test for patency of deep veins. Most of the patients seen have already had vein injections or saphenous vein ligations. If not, these procedures should be considered. Control of the local infection is of the utmost importance.

The ulcer must be debrided by floating the area with a solution of 3 per cent hydrogen peroxide, and by means of sharp thumb forceps peeling off crustations and devitalized tissue. Aureomycin ointment is applied to the ulcer. The ulcer is covered with a 3- by 3-inch sterile gauze square and the leg from knee to ankle is wrapped with a 3-inch elastic bandage. No tape is used to hold on the gauze square. The patient is instructed to wash the ulcer twice daily at home with hydrogen peroxide and reapply aureomycin ointment. The elastic bandage is worn day and night except for two hours during the day when the patient is instructed to air dry the ulcer while the leg is elevated.

Infrared radiation is given over the ulcer area at two feet distance for 10 minutes daily. This procedure is followed for two weeks during which time the infection usually clears nicely. The patient notices less discharge and pain. Healing is evident by the appearance of healthy granulation tissue at the base of the ulcer.

The patient is given papaverine hydrochloride 1 gr. three times a day from the first day of treatment. Papaverine aids local circulation in the ulcer area by relieving spasms of the arterioles. If diabetes mellitus is present, insulin treatment is initiated immediately. All smoking, alcoholic beverages, and coffee, tea and spiced food are forbidden. Postural exercises are encouraged. EMPIRIN® with codeine ½ gr. is given to control the pain, which frequently is very severe.

After supportive and local treatment has controlled the infection present, a second procedure is followed. I do not favor continued ointment treatment of indolent ulcers because the grease base of the ointment keeps the ulcer too moist, and stimulates excessive secretion. The goal is to dry out the ulcer, keep down the secretion, allow a solid crustation (scab) to form, sealing in the area and protecting the young blood vessels. This process assures healthy cicatrix formation. Likewise, I do not favor use of an elastic bandage after the first two weeks or so. The elastic bandage support is not maintained from day to day due to slippage as many patients are not able to roll on the bandage properly. For these reasons after two weeks a different procedure is followed—an Unna boot is applied.

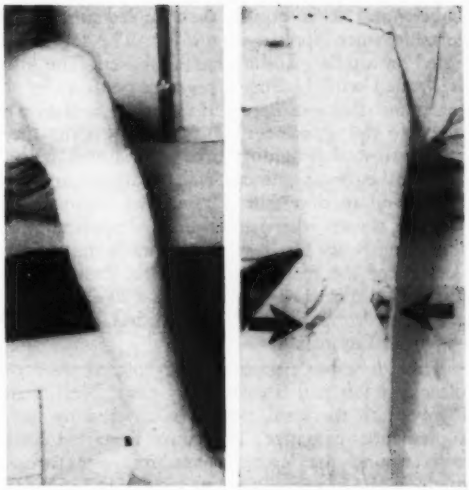

FIGURE 1 *(left)*. This is the position of the leg for application of the Unna boot. The figure above shows a completed boot. FIGURE 2 *(right)*. Leg after the Unna's paste has been applied showing the ulcers and narrow margin around them left uncoated.

APPLICATION OF UNNA BOOT

The Unna boot is an elastic tailored bandage, applied to conform with the contour of every shape of leg, giving the ultimate support around the clock, without slippage. I find that making my own boot gives the best results, rather than using the gauze which is already impregnated with Unna's paste.

Necessary equipment for applying Unna's boot:

1. Unna paste.
2. Double boiler.
3. Electric plate or other means of heating the paste.
4. 2-inch paint brush.
5. Three 2-inch gauze rolls.
6. 3 by 3 sterile squares.
7. 5 per cent aqueous gentian violet.
8. Adhesive tape strips one-half inch wide.
9. Razor.

Formula—Modified Unna's paste.

Zinc oxide	20 gm.
Gelatin	40 gm.
Glycerin	80 cc.
Water	80 cc.
Calamine	30 gm. to 1 lb.

Procedure—Unna's paste is heated in a double

boiler until it is liquid, then cooled until comfortable when applied to the leg. The leg is elevated on a pillow and all hair is shaved. The ulcer is cleaned with hydrogen peroxide with an applicator and the area debrided. Infrared radiation is given to the area for 10 minutes. Then the ulcer and narrow surrounding area are painted with 5 per cent aqueous gentian violet solution and this is allowed to dry. The patient then assumes the position shown in Figure 1 for the application of the Unna boot. The leg from beneath the knee to dorsum of the foot is painted with Unna's paste, applied by means of a paint brush. The ulcer area and a small margin around it are left uncoated as shown in Figure 2.

Then, a 3 by 3 gauze pad is placed over the ulcer and this pad is covered by paste. Next, starting beneath the knee, the leg is covered by interrupted turns of gauze. The gauze is started clockwise around the leg, and one complete turn is made with enough overlapping of the gauze to fasten in the starting end. Each turn is then cut and a new turn started beneath so that the gauze overlaps at the upper turn.

These interrupted turns are continued down the leg to the ankle. At this point, the turns are made to go around the plantar surface of the foot and back to the ankle to secure the boot to the bottom of the foot and prevent its creeping upward. The first layer having been completed, another coat of Unna's paste is applied, this time over the gauze which is covered and impregnated.

Then the second layer of gauze is applied, this time in a counterclockwise manner and likewise in interrupted turns around the leg. The second layer completed, a third layer of gauze is applied by continuous turns, with a half twist to allow the gauze to comply with the curvature of the leg and ankle. Adhesive strips are then applied, one clockwise from the knee to the foot and the other counterclockwise. The tape must never touch the skin. Most of these patients show hypersensitivity to tape on the extremity involved. Tape elsewhere might not give any difficulty. After allowing some time for the paste to dry, the patient is able to be up, about and working. He returns for treatment weekly. When the patient returns, the boot is removed by cutting with bandage scissors much in the same manner as a cast is removed. The boot usually is removed with ease leaving the leg clean.

If the ulcer is stuck to the gauze, the area is saturated with 3 per cent hydrogen peroxide and the stuck area will easily be freed. The excess paste is easily removed by means of ether.

The ulcer is cleaned with hydrogen peroxide, the area debrided of crustation and devitalized tissue. Infrared radiation is given to the area. Then 5 per cent aqueous gentian violet solution is applied to the ulcer and the boot is reapplied. This process is continued weekly until the healing is completed.

Recently, I have been applying the boot to all areas around the ulcer, but leaving a window over the ulcer. This is easily done by carrying the gauze turns above and below the ulcer. This allows for daily cleaning of the ulcer and infrared radiation. The window is covered by sterile gauze squares and a few turns of elastic bandage. I have found that the best time to apply the windowed boot is after several complete boots have been applied, and healing is evident.

Eight to ten weeks is the average length of time needed for treatment. After the ulcer has healed, the patient is instructed to keep the leg wrapped with a three-inch elastic bandage for two months or longer while working.

Occasionally secondary eczema develops around the ulcer area. This is treated by soaking with potassium permanganate (1:1000) after the ulcer has healed, plus light skin doses of x-ray. Usually the eczema responds quickly. Oil of theobroma (cocoa butter) applications (after the ulcer has healed and the crustations have fallen) aids a great deal in softening the cicatrix formed and makes the skin more pliable, preventing any cracking due to movement.

SUMMARY

Indolent ulcers with different etiologies have been successfully treated as follows: 1. By Unna boot supportive treatment—allowing ambulation during treatment.

2. Local care of the ulcer by means of aureomycin ointment for infection, infrared radiation, and 5 per cent aqueous gentian violet, locally to stimulate tissue growth.

3. Papaverine hydrochloride ½ gr. three times a day orally.

4. Abstinence from alcohol and spiced foods.

5. Insulin control of the diabetic.

6. Oil of theobroma locally to cicatrix to aid in keeping skin pliable, and to prevent cracking.

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Nutritional Management of Infants and Children

ROBERT L. JACKSON

STATE UNIVERSITY OF IOWA, IOWA CITY

JACKSON

KNOWLEDGE has increased rapidly in the present century requiring many changes in our methods of nutritional management of infants and children. We have learned that the condition of the mother during pregnancy affects the health and welfare of her baby and that infants are not "born equal" insofar as the storage of nutrients is concerned. Artificial feeding of infants has become so easy and successful that the importance of breast feeding is underestimated and needs to be restressed. Foods other than human milk or suitably modified cow's milk have been added to the infant's diet closer and closer to the time of birth in order to meet known nutritional needs. In general, our increased nutritional knowledge is receiving greater application in feeding of infants than for older children. Four nutritional essentials require special emphasis in childhood, namely protein, calcium, vitamin D and the B group of vitamins.

*Associate Professor, Department of Pediatrics, State University of Iowa, Iowa City, Iowa.

Studies of diets of pregnant women show that the poorest dietary habits are found among the very poor and the very rich, also that the large group in between these two categories could be better fed than they are in protein, calcium, vitamin D and probably the B group vitamins. The last-named are usually provided in excess as pharmaceutic products. The same money spent for meat and milk would make the diet more nearly adequate in all essentials. Particularly the idea prevalent among some doctors that calcium salts are a complete substitute for milk deprives the mother of excellent protein, vitamin A, riboflavin and some thiamine, all at considerable expense to herself.

THE PREMATURELY BORN AND IMMATURE INFANT

Nearly half of the protein and calcium of the newborn infant is deposited during the last four weeks of gestation. Although human milk is admirably adapted for the full term baby, it will be impossible for the prematurely born infant to "catch up" if fed only human milk. It is therefore desirable to add dry skimmed milk or calcium caseinate to human milk or to use a modified cow's milk formula. Because of the susceptibility of the prematurely born infant to rickets, it has

been the practice of most physicians to give large amounts of vitamin D. Recent studies show that the prematurely born baby requires no more vitamin D than does the baby born at term. Increased vitamin D does not compensate for the low mineral intake.

The prematurely born infant is particularly prone to rapid changes in water metabolism and becomes dehydrated or edematous far more quickly than the full term infant. The kidneys of the premature infant are incompletely developed and cannot concentrate urine, so the water requirement is relatively high. The total amount of fluid needed in 24 hours is approximately 150 ml. per kilogram of body weight and the basic chloride requirement is supplied by approximately 100 ml. of normal saline solution.

The prematurely born baby's enzyme systems are incomplete. Oxidation of carbohydrates may not proceed to carbon dioxide and water but stop with the formation of organic acid, as lactic and pyruvic acids. Sodium citrate, therefore, is a better agent to modify the curds of cow's milk in feeding of prematurely born infants than is citric or lactic acid. One teaspoonful of 25 per cent solution is sufficient for a quart of milk or 1 gr. of powdered citrate to each 2 ounces of milk. Certain of the amino acids, particularly phenylalanine, are metabolized with difficulty by prematurely born infants. It has been found that the addition to the diet of a larger amount of vitamin C (50 mg.) aids in oxidation.

BREAST FEEDING

Despite all our knowledge of infant nutrition and the current refinements of artificial feeding, feeding at the breast of the mother continues to offer definite advantages to both mother and infant.

Many influences have crept into modern living to sway the mother from breast feeding her child. There are those mothers who have accepted the common practice of artificial feeding as more convenient and adapted to their way of living and many who do not understand and have not had the advantages of breast feeding explained to them. More frequently than is recognized the father is the strong advocate for artificial feeding for many unsound reasons. Breast feeding cannot be done by the unstable or selfish mother nor without the active support of husband and doctor. Parents cannot learn too soon that they must give of themselves to provide emotional growth of their child.

The social trend toward hospitalization for childbirth has moved amazingly fast in this country. This trend has been accompanied by a substantial decline in breast feeding. In many hospitals the conditions of crowding, lack of trained personnel and inadequate equipment make the possibility of introduction and spread of infection in the newborn nursery a constant danger. This fear of infection and hospital convenience have made present day nurseries overmechanized, and the whole procedure has become artificial.

Breast feeding on a self-demand basis is the ideal procedure. A hospital procedure such as "rooming-in" promotes natural happy relationships, fosters maternal nursing, and the father has a chance to enter the family circle at an earlier time and to become acquainted with the baby. Too frequently our hospitals are so depersonalized and mechanized that the parents feel acutely that the institution exists for the sake of procedure and personnel rather than for the care of the mother and baby. It is a deplorable commentary that it is taking infection, morbidity and lack of hospital personnel rather than common sense to put babies back with their mothers.

Preparation of the mother for nursing her baby must start under the direction of her physician early in pregnancy. The prospective mother must be educated to understand the importance of breast feeding. In advising breast feeding, care must be taken not to impress the importance to such a degree that the mother will feel inadequate or blameworthy if it becomes impossible for her to nurse her baby.

ARTIFICIAL FEEDING

When an infant is deprived of human milk, cow's milk easily can be modified to meet the infant's nutritional needs. The amount of fresh cow's milk given the young infant should approximate 1.5 to 2 ounces for each pound of expected body weight. The amount of carbohydrates added should approximate 6 to 8 per cent of the total quantity of milk. The amount of water to be added depends on the degree of dilution required to render the formula readily digestible. It is my preference to use fresh boiled cow's milk with a low fat content for the first few weeks or months after birth and to compensate for the loss of calories by giving added carbohydrates.

If the infant shows any signs of intolerance, the formula can be rendered more digestible by acidification. Acidified milk is so easily digested that dilution rarely is necessary for feeding even young infants. Mixtures of this type are of special value for the feeding of infants who regurgitate when larger volumes of food are taken. In the preparation of acidified milk approximately 100 drops of lactic acid (U.S.P. 85 per cent) or 1 teaspoonful of a 25 per cent solution of citric acid or 2 teaspoonsful of 36 per cent acetic acid U.S.P. or 6 teaspoonsful of lemon juice are sufficient for each quart. After infants weigh approximately 10 pounds the likelihood of their not tolerating an evaporated milk formula is negligible. Consequently at this time I prefer to change to a diluted evaporated

milk type of feeding and to decrease gradually the dilution and carbohydrate content of the formula as tolerance increases and solid foods are introduced into the diet.

SUPPLEMENTS

Milk from a healthy mother who has had a good diet meets all the nutritional needs of her infant in the early months of life with the exception of vitamin D. Four hundred units of vitamin D are advocated for the breast-fed infant each day. During the early weeks after birth I prefer to give the baby a concentrated vitamin D preparation which can be administered as drops into the baby's mouth. The mother must be cautioned to use only the number of drops prescribed, as there is a tendency for her to believe that if a little is good, more would be better. As soon as the mother is secure with her infant, I advise that she gradually replace the concentrated vitamin D preparation with plain cod liver oil, beginning with a small amount and gradually increasing to a teaspoonful a day. The baby will learn quickly to suck it off the tip of a spoon.

The infant fed human milk does not need added vitamin C as early as the artificially fed infant provided the mother's diet has a liberal supply of vitamin C. However, vitamin C is a harmless safeguard for the breast-fed infant, and it is good pediatric practice to give the infant small supplements of orange juice beginning in the early months after birth.

Too often administration of vitamin D, and in the case of artificially fed babies, of vitamin C, is delayed even into the second month, and when they are started, the amount of vitamin C may be too small and the amount of vitamin D may soon become excessive. Maximum calcium and phosphorus retentions are obtained with 300 to 400 units of vitamin D daily. Not only are retentions no greater with any larger amount, but with the use of 1800 units or more daily for several months appetite is decreased and as a consequence total retentions of calcium and phosphorus are decreased and linear growth is slowed. One ounce of orange juice (15 mg. of vitamin C) is sufficient for infants to 3 months of age.

Overdosage with fat-soluble vitamins A and D can and does occur and should be avoided. The toxic level of vitamin A is not known but is much higher than that of vitamin D. Nevertheless acute toxicity has occurred from overdosages. Amounts of vitamin A equivalent to five times the vitamin D dosage may be added to the vitamin A content of the feeding with impunity as far as the effect on growth, development or appetite of infants is concerned.

The requirements of the full term infant for calories, protein, calcium and phosphorus, sodium, potassium, water, riboflavin and vitamin A will be met when the breast-fed infant receives 2 to 2½ ounces of milk per pound and the infant fed cow's milk gets 1½ to 2 ounces per pound of body weight of milk containing 6 to 8 per cent added carbohydrate. The requirements for thiamine and niacin are probably met. Additions of foods containing iron and thiamine are desirable by 3 months or soon thereafter.

IRON

Neither human nor cow's milk provides an adequate source of iron for the infant. The chief source of iron for the baby during his first six months is the extra hemoglobin present in the blood at birth. The volume of blood of the new infant is influenced greatly by when the umbilical cord is clamped If the cord is not clamped until pulsations cease, the infant receives up to 100 cc. more blood than when the cord is clamped early.

After 5 to 6 months of age, the hemoglobin value reflects the dietary regimen. It appears wise to begin the additions of iron-containing foods at the time when the infant reaches his minimum hemoglobin level (2½ to 3 months). The common iron-containing foods fed to young infants—egg yolk, green vegetables—provide 1 to 2 mg. daily at most. The sieved meats provide 0.5 to 1.7 mg. to the ounce. Many of the special infant cereals have iron added in amounts providing 2.5 to 4 mg. to the serving of 1/3 ounce. Infants receiving no supplementary food source of iron have maintained normal hemoglobin when 5 to 12 mg. of iron are given in the milk of their diet. In adding iron salts to the diet, 0 5 mg. as iron per pound of body weight can be considered a good prophylactic amount.

THIAMINE

The thiamine content of human milk varies widely, being dependent on the mother's diet; the average value is low, 0.13 mg. to the quart. Cow's milk contains 0.38 mg. to the quart, but its thiamine is partially destroyed by heating, so that an infant fed a diluted milk formula may get little more than the breast-fed infant. The minimum requirement is considered to be 0.24 mg. per 1000 calories, so the average thiamine intake must be considered as barely adequate. It seems desirable, therefore, that the supplementary foods given earliest be those contributing thiamine as well as iron to the infant diet.

SOLID FOODS

Solid foods should be introduced to the infant in the third or fourth month after birth. Egg yolk in the form of a soft custard provides a suit-

able preparation for this purpose. Sieved meats especially prepared for babies can be substituted for the egg yolk if there is a definite family history of allergy. There is an advantage in giving sieved vegetables and fruits early to provide variety in flavor and texture. The most important advice to give the mother is that the baby probably will show little desire for new foods the first few times they are offered.

Although nutritional knowledge has increased rapidly, there is evidence that our present knowledge is incomplete. Varieties of fruits, vegetables and meats would seem to offer better opportunity for a mixed assortment of food sources than the more limited varieties of cereals used in infant feeding. Cereal feedings should not be large nor be offered more than once a day.

As the baby becomes older, it is desirable gradually to offer the solid foods in a coarser form. At approximately 5 months of age, the baby should be offered some of his milk from a small glass or cup, and weaning should proceed gradually over a long period of time. The continuance of bottle feeding after the first year under ordinary circumstances is not good feeding practice.

In recent years the most common problem for which older infants and children are brought to the pediatrician is anorexia, usually dependent upon faulty training in feeding habits during infancy. The interrelationships which are set up between mother and child during the early days and weeks of life set a pattern which is important for the later development of the child. The mother who nurses her baby establishes at an early date an intimacy with her child which makes future relationships with him easy and natural. This is one of the major advantages of breast feeding, which recently has been stressed by many authorities. Too often a definite volume of food is prescribed by the physician, and the conscientious and solicitous parents endeavor to give this exact quantity of food at each feeding regardless of possible variations of appetite. Rebellion against food most frequently has its beginning in this manner. Self-demand feeding schedules have been advocated to overcome this difficulty, but common sense is required by the parents in using such a schedule, because too frequently the baby is fed every times he cries, which again leads to faulty feeding habits. In other words, either extreme—too rigid a schedule or no schedule—can easily lead to difficulties.

The emotional health of the parents to a great extent determines the likelihood of a feeding problem arising in the infant. This means that there is no simple or uniform manner to avoid these difficulties. Physicians' responsibility in proper feeding of infants includes psychologic treatment of the parents. It is for this reason that frequently a history is obtained of a healthy infant who is not thriving on a nutritionally adequate diet which has had many minor alterations by a conscientious physician. The problem is not the tolerance of the formula by the infant, but rather the adjustment of the parents in taking care of their baby.

FEEDING OF CHILDREN

The nutritional management of infants has received much greater attention by doctors and parents than nutritional management of children past infancy. Vitamin D, calcium, protein and the B group of vitamins are commonly deficient in the diet of the child.

Without vitamin D children vary widely in their ability to use calcium and phosphorus. Three to four hundred units of vitamin D daily will produce adequate retention of these minerals. Except for therapeutic purposes and to supply vitamin D, no known need exists for special vitamin preparations in the feeding of healthy children. Too often excess vitamins are provided as pharmaceutic products. The same money spent for milk and meat would make the diet more adequate in all of the essentials.

Calcium is the mineral most likely to be deficient since other essential minerals are more likely to be present in most diets. Milk and milk products are our best sources of calcium. Milk, however, should not be considered solely as a source of calcium as it contributes most importantly to the requirement of protein as well as other essentials. During the period when the calcium requirement is lowered, the requirement for protein is high. Hence, it is advisable to suggest 1 to 1½ pints of milk after the period of infancy and up to the age of approximately 10 years and a quart or more during the period of the prepubescent spurt.

Protein deficiency is much more common than is generally appreciated. The height and weight of the child are not criteria for judging protein metabolism. Without the inclusion of milk in the diet, the protein requirement of the child cannot be met unless special and expert supervision is given. A quart of milk daily supplies most of the protein need of the young child and half the need at the beginning of adolescence.

Meat, particularly pork and the glandular organs, and eggs are good sources of the B group of vitamins. A child who drinks his allowance of milk receives most, if not all, of his requirement of riboflavin. Consequently if the child is receiving a good intake of protein from milk, meat and eggs the likelihood of deficiency of the B group of vitamins is negligible.

Vitamin B preparations are used commonly for their effects on appetite. Anorexia in children is a common symptom for which medical advice is sought. Correcting the environment and faulty

feeding habits of the child is the answer to the problem rather than prescribing a vitamin B preparation.

Deficiencies in the diet frequently arise because sugar in the form of candy, soft drinks and other confections and refined cereal products replace nutritionally valuable foods in the diet. Replacing candy and soft drink machines in schools with food bars dispensing milk and other protective foods would greatly improve the nutritional status of many children.

Much evidence exists that the nutritional management of infants and children can be greatly improved if our present knowledge is applied.

Pediatric Anesthesia

C. R. STEPHEN*

DUKE UNIVERSITY, DURHAM, NORTH CAROLINA

STEPHEN

TWENTY years ago the anesthetist was concerned principally with keeping the patient asleep and providing muscular relaxation for the surgeon. Today his horizon and duties have broadened to include the maintenance of the patient in a state as close as possible to the physiologic normal during operation. This implies adequate oxygenation at all times, avoidance of deep planes of anesthesia if possible, prevention of gaseous acidosis by not allowing accumulation of carbon dioxide, elimination of metabolic acidosis by proper choice of agents, and replacement of fluid—be it water, plasma or blood—as it is lost in the operating room.

In pediatric anesthesia, fulfillment of the above requisites may be difficult. A rather crude but apt simile is that of the anesthetist and his patient compared with a chauffeur and his automobile. One must think of a driver handling a small bantam car. These cars do not travel over rough roads smoothly; they must be driven skilfully at all times or they will skid off the highway and be wrecked. They often develop engine trouble with less provocation than do larger cars; at the same time their consumption of gasoline is less than that of their big brothers.

Similarly the anesthetist dealing with children realizes that the road of anesthesia between unconsciousness and death may be short and fraught with many perils and that his utmost attention is required to avoid respiratory, neurologic and circulatory complications. After watching a sleeping child for a few moments, one is impressed by the small exchange of air that occurs with each breath and with the relative frailty of the muscles responsible for respiration. How important it becomes to make certain that during anesthesia nothing is done to obstruct that exchange of gases, to impede the airway or to diminish the action of the respiratory muscles! If the muscles become fatigued—as they may in long operations—or if their work becomes ineffective by employing agents depressant to their end-organs (curare), or to the respiratory center (PENTOTHAL,® cyclopropane), there must be no hesitation in aiding or assisting their action by manually inflating the lungs during inspiration. Only in this way can hypoxia and accumulation of carbon dioxide be avoided.

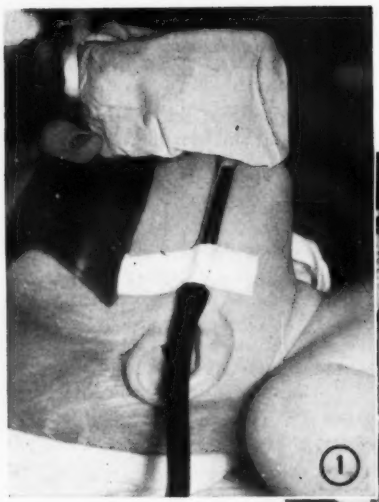
*Associate Professor of Anesthesiology and Chief, Division of Anesthesia, Duke University, Durham, North Carolina.

PREMEDICATION

Since emotional conflicts in later life may stem from disturbing experiences in youth, proper psychic preparation of the child prior to surgery is important. Fear is the principal emotion to be combated, and most of it springs from fear of the unknown. Tell a child truthfully what is going to happen, make no heroics concerning the situation, allay any tendency to alarm by preoperative sedative drugs (Table 1), and psychic trauma will be minimized. Doting parents who insist on coming to the operating room saying, "It won't hurt, Jimmie, everything will be all right," only confuse the child and arouse apprehension.

AGENTS

One of the oldest and probably the safest anesthetic at our disposal is ethyl ether, and one of the



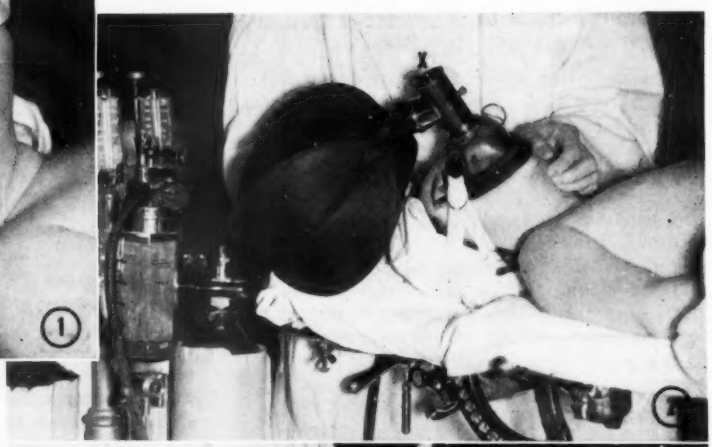


FIGURE 1. Open drop technic for ether administration. Insufflation of oxygen via mouth hook.

FIGURE 2. Partial rebreathing, or fractional, technic. Total gas flow is eight liters per minute, with 25 per cent oxygen. Exhalation through valve X at top of chimney.

FIGURE 3. Non-rebreathing technic, showing reservoir bag, non-rebreathing valve. All exhalations through valve A. Dead space from A to endotracheal tube is 9 cc.

most common methods of administering it to children is by the drop method on some type of mask (Figure 1). It is one of the few agents available which, in "surgical" planes of anesthesia, cause little depression of respiration. Even if an overdose sufficient to produce respiratory arrest is given, there is time for resuscitation before cardiac failure occurs. Because of the peculiar odor, respiratory tract irritation and sense of suffocation associated with its use, induction may be laborious for both patient and anesthetist. Induction is shortened and less tumultuous if the potent agent, vinyl ether (VINETHENE®), is employed prior to ethyl ether. By dropping, never pouring, vinyl ether on the mask, unconsciousness is produced in one to two minutes. It may be used as a sole anesthetic agent for short procedures lasting less than 10 minutes.

A warning should be given concerning another potent induction agent, ethyl chloride. Its properties are closely allied to those of chloroform, and respiratory and cardiac arrest may occur with as few as three or four inhalations of its vapor. There is no indication for its utilization when the safer vinethene is available.

Under drop ether anesthesia, hypoxia may develop though the airway is clear and respirations not depressed. This is explained by recalling that ether vapor must be supplied in a concentration of four to six volumes per cent for maintenance of anesthesia; also it is known that the area under

TABLE 1

PREOPERATIVE SEDATIVE DRUGS

AGE	DEMEROL®	SCOPOLAMINE
(Years)	*(Milligrams)*	*(Grains)*
1-2	13	1/450
3-4	18	1/450
5-6	25	1/300
7-8	37	1/300
9-12	50	1/300
13	75	1/200

the mask acts to some extent as dead space, and so a certain amount of expired air, deficient in oxygen, is inhaled with each inspiration. These two factors serve to dilute the inspired oxygen, so that less than 20.9 per cent is being breathed.[1] This hazard may be obviated by insufflating oxygen at a rate of one to two liters per minute under the mask. By the same maneuver the possibility of carbon dioxide accumulation under the mask may be avoided.

If upper respiratory obstruction develops during anesthesia, and is not eradicated by proper holding of the jaw, insertion of an oropharyngeal airway or aspiration of offending secretions, serious consideration should be given to the insertion of an endotracheal tube. Instigation of chronic hypoxia by persistent upper respiratory obstruction is a greater risk to the child than any problem associated with intubation. Plastic portex tubes rarely precipitate any local irritation of the larynx or trachea.

TECHNICS

The modern anesthetic gas machine was built to facilitate the administration of gases such as nitrous oxide and cyclopropane, as well as of vapors such as ether. It was constructed primarily for adult use, and the presence of soda-lime canisters, directional valves and long accordion conduction tubes provide a resistance to the flow of gases sufficient to fatigue quickly the muscles of the small child.[2] It is unwise to employ such machines in the "closed absorption" technic for children under 7 years of age. If the benefit of gaseous mixtures is desired, the partial rebreathing, or fractional, technic is preferable (Figure 2), provided that high flows of gases are used to minimize the possibility of rebreathing. The most physiologically sound technic for employing gaseous mixtures is embodied in the non-rebreathing valve[3] (Figure 3), which functions with practically no resistance to inspiration or expiration, and which prevents accumulation of carbon dioxide by removing exhaled gases from the circuit completely.

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Intestinal Obstruction in the Newborn

JULIUS B. RICHMOND AND STERLING D. GARRARD*

UNIVERSITY OF ILLINOIS COLLEGE OF MEDICINE, CHICAGO

CONGENITAL anomalies now constitute the second most frequent cause of infant mortality. Since intestinal obstruction in the newborn infant is almost always caused by congenital anomalies, prompt and accurate diagnosis and proper management are destined to play an increasingly significant role in the reduction of infant mortality.

Diagnosis—The management of intestinal obstruction in the newborn infant cannot be discussed without a brief consideration of diagnostic procedures. The diagnosis may be suspected in any infant with vomiting and abdominal distention in the first 24 hours of life.[1] If the intestinal obstruction is high, distention may not be marked and may be limited to the left upper quadrant. A plain film of the abdomen will outline distended loops of intestine *without the use of contrast media* and will be highly diagnostic. Barium sulfate as a contrast medium is potentially hazardous since

*Department of Pediatrics, University of Illinois College of Medicine, Chicago, Illinois.

TABLE 1

INTRAVENOUS FLUID AND ELECTROLYTE THERAPY PER TWENTY-FOUR HOURS FOR MAINTENANCE OF THE NEWBORN INFANT

SOLUTION	CUBIC CENTIMETERS	DILUTION AND RATE OF ADMINISTRATION	CONTENT OF DILUTED OR CONCENTRATED SOLUTION							
			Sodium (mEq.)	*Potassium (mEq.)*	*Chloride (mEq.)*	HCO_3 *(mEq.)*	*Glucose*	*Protein*	*Cal.*	*Water*
Darrow's solution* or	30-60 total	Dilute with 3 parts 10% glucose. Rate, 15 drops per minute	4-8	1.2-2.5	3.5-7	1.6-3.2	Approx. 9-18 gm.		Approx. 36-72	120-240 when diluted as suggested
0.85% sodium chloride† ("normal" saline)	30-60	Add 6-12 cc. 50% glucose to make a 10% solution of glucose in saline	4.5-9		4.5-9		3-6 gm. if concentrated glucose is added		12-24	Approx. 30-60
5% amino acids (salt-free) and 5% glucose	Between 285-500. Quantity sufficient to meet fluid requirements after one of above solutions	Add 50% glucose to bring glucose concentration to 10%. Rate, 15-20 drops per minute	Salt-free				Approx. 28-50 gm.	14-25	168-300	Between 285-500. Quantity sufficient to fulfill fluid requirements
Whole blood‡ as indicated	10-15 cc. per pound		14 per 100 cc. (serum)	0.4-0.5 per 100 cc. (serum)	10 per 100 cc. (serum)	2.6 per 100 cc. (plasma)		5 gm. per 100 cc. (serum)	0.2 cal. per cc.	Approx. 55 cc. per 100 cc. whole blood
TOTALS PER 24 HOURS			4-9	1.2-2.5	3.5-9			2-3 gm. per pound	36-46 per pound	75 cc. per pound (approx. 525)
REQUIREMENTS PER 24 HOURS			4.5-9	1.2-2.5	3.5-7			1.5 gm. per pound	45-55 per pound	75 cc. per pound (approx. 525)

*Available commercially. Composition (milliequivalents per liter): sodium, 122; potassium, 37; bicarbonate, 52; chloride, 107.

†If maintenance therapy is necessary longer than two to three days, Darrow's solution should be used.

‡Not included in 24-hour totals in table. When whole blood is used in therapy, allowances must be made for electrolyte, protein, caloric and fluid content.

its aspiration into the tracheobronchial tree in a vomiting infant is very likely. Chemical pneumonitis, which is usually fatal, results.

It is an important physiologic fact that gas appears normally throughout the intestinal tract (as observed by roentgenographic examination) in the first 6 to 12 hours of neonatal life without producing distention. The extent of distended intestinal loops may permit rather accurate speculation concerning the site of obstruction. These findings have been described very well in an article by Storch et al.[2]

The most common sites of obstruction in the newborn period are the duodenum, ileum and anorectal region. The possibility of multiple obstructions should be kept in mind. Since pancreatic insufficiency (cystic fibrosis of the pancreas; mucoviscidosis) produces meconium ileus when it presents itself in the newborn period, it must be considered in the differential diagnosis of intestinal obstruction in this age group. Tenacious, rope-like meconium, when combined with radiographic findings of "bubbles" in the gas pattern as described by Neuhauser,[3] is highly suggestive of the diagnosis. The stools do not digest gelatin on unexposed x-ray film as Schwachman et al. have recently reported.[4]

Complete obstruction may be verified by Farber's test.[5] This test is based upon swallowing by the fetus of amniotic fluid and vernix containing epithelial cells. These cells appear in meconium if the intestinal tract is patent and may be ob-

TABLE 2

ANTIBIOTIC AND SULFONAMIDE DOSAGE IN THE NEWBORN

DRUG	TOTAL 24 HOUR DOSAGE	INTERVAL AND ROUTE
Crystalline penicillin	3000 to 5000 units per kilogram of body weight	Intramuscularly every 6 hours
Procaine penicillin	150,000 units	Intramuscularly once every 24 hours
Streptomycin and dihydrostreptomycin	10 to 15 mg. per kilogram of body weight	Intramuscularly every 6 hours
Chloramphenicol (CHLOROMYCETIN®)	25 mg. per kilogram of body weight	Orally every 6 to 8 hours
Aureomycin	25 mg. per kilogram of body weight	Orally every 6 to 8 hours
Aureomycin in l-leucine diluent	10 to 15 mg. per kilogram of body weight	Intravenously once or twice in 24 hours
Terramycin	25 mg. per kilogram of body weight	Orally every 6 to 8 hours
	10 to 15 mg. per kilogram of body weight	Intravenously once or twice in 24 hours
Sulfadiazine and sulfamerazine (equal parts of each as a 5 per cent solution in distilled water)	0.032 gm. per pound of body weight (½ gr. per pound)	Subcutaneously once in 24 hours
Triple sulfonamide mixture (sulfadiazine, sulfamerazine, SULFAMEZATHINE®)	0.100 gm. per pound of body weight initial dose; 0.064 gm. per pound maintenance dose	Orally every 12 hours after priming dose

served if properly stained. Often, however, the diagnosis is evident without recourse to this test.

TREATMENT

The definitive treatment of complete intestinal obstruction must be surgical. In general, relief of obstruction can be effected by the skilful surgeon who respects the delicate tissues of the newly born infant. Thus, malrotation resulting in obstruction can be relieved, congenital bands constricting the intestine or predisposing to volvulus may be appropriately interrupted, atresias may be short circuited by primary anastomosis and extrinsic masses may be removed or their effects minimized. When meconium ileus is present, surgical intervention may be advisable in order to relieve obstruction produced by tenacious meconium.

The surgeon should be absolutely certain that multiple obstructions are not present to prevent the manifestations of intestinal obstruction from reappearing. Contrary to popular belief, newly born infants tolerate surgery remarkably well[6]; procrastination after the diagnosis has been established, except for restoration of fluid and electrolyte balance, will increase mortality. With the lapse of time the hazards of intestinal distention, possible perforation and toxemia become more pronounced.

Although the surgical procedure is important, perhaps the greatest reduction of mortality has resulted from improvement in supportive measures. Since these measures apply equally to preoperative and postoperative care, they will be presented without separate reference to each period.

Intestinal decompression—Reduction of intestinal distention while preparing the infant for surgery and in the postoperative period may be life saving. The relatively thin intestinal wall in infants predisposes to perforation with resultant peritonitis if distention is uncontrolled. Less commonly appreciated is the fact that intestinal distention may significantly interfere with respiratory excursion. Cyanosis may result but can frequently be relieved by intestinal decompression.

We prefer to introduce a soft rubber catheter (No. 8 French) into the stomach and to attach it to a source of *gentle* suction. To minimize trauma to the gastric mucosa we prefer to produce multiple small perforations (20 to 30) in the catheter tip with a red hot pin rather than to cut the customary large holes with scissors. Although it is possible to effect intestinal intubation for purposes of decompression, we have not found this necessary since good results are usually obtained with gastric suction. In addition, passage of an intestinal tube may delay surgery.

Postoperatively the importance of protecting the suture line at the site of anastomosis by decompression is well known. Oral feedings are not begun until clamping of the gastric tube for several hours does not produce distention. This may vary from 24 hours to several days and is usually dependent on such factors as the degree of intestinal manipulation, the presence of perforation at the time of surgery and the extent of the surgical procedure. *Oral feedings should not be started until the infant is free of distention.* Violation of this rule is one of the most frequent causes of postoperative difficulty.

Oxygen—The maintenance of relatively high oxygen concentrations in the inspired air is significant in reducing respiratory distress. Its effects in minimizing intestinal distention are probably secondary in this age period. An oxygen tent is the only practical way by which this can be effected in infants. Failure to humidify the oxygen is a common error. Drying and inspissation of tracheobronchial mucus result (especially following anesthesia) and predispose to atelectasis. The hazards of this complication are well appreciated.

Fluid and electrolyte therapy—Advances in the maintenance of fluid and electrolyte balance have undoubtedly played an important role in reducing mortality from intestinal obstruction in the newborn. Maintenance requirements of fluid and electrolytes are presented in Table 1. It should be remembered that these are *maintenance* requirements only, and that additions and modifications are necessary depending upon fluid losses resulting from vomiting, diarrhea or suction.

Clinical observations of tissue turgor, mucous membranes and fontanel tension are helpful in assessing the infant's state of hydration. Laboratory determination of the carbon dioxide combining power and serum chloride, sodium and potassium may be very helpful in determining the precise electrolyte composition of fluids to be administered. Serial hematocrit determinations and red blood cell counts provide an index of hydration and indicate the need for whole blood infusions.

Failure to appreciate the physiologic immaturity of renal function in the newborn is a common error. Postoperative diminution of renal function may be superimposed on this immaturity and interfere with renal regulation of electrolytes and water. Thus, excessive quantities of sodium-containing fluids may be given with the production of generalized edema. Blood and plasma may be administered as clinical conditions indicate.

A cannula placed in a vein for fluid administration during surgery is essential and can be used for replacement of blood as necessary. Postoperatively phleboclysis should be continued; the subcutaneous route cannot be relied on for complete satisfaction of fluid and electrolyte requirements. For details concerning fluid and electrolyte balance the reader is referred to a discussion by Butler.[7]

Antibacterial therapy—Because of the hazards of peritonitis, antibacterial therapy is indicated when the diagnosis is established. Although possessing a broad antibacterial spectrum, available preparations of aureomycin, CHLOROMYCETIN® and terramycin are not suitable for subcutaneous or intramuscular injection. Thrombosing effects of aureomycin on veins render it disadvantageous for extended intravenous use. As a result a combination of intramuscular penicillin and streptomycin (the latter for several days only) is commonly employed by us. Occasionally sulfonamides are used; we have maintained good therapeutic levels with a mixture of sodium sulfadiazine and sodium sulfamerazine (2.5 per cent of each in distilled water to make a 5 per cent sulfonamide solution) as a single subcutaneous injection once every 24 hours.[8] The dosage is 0.032 gm. per pound of body weight.

Limitations of renal function permit a longer interval between doses of all antibacterial agents when employed in early infancy. Whenever possible, peritoneal cultures should be made at the time of surgery as a basis for selection of specific antibacterial agents. Generally recommended dosage schedules are presented in Table 2.

General considerations—The possibility of hemorrhage resulting from hypoprothrombinemia may be anticipated in infants during the newborn period and should be avoided by administering 1 mg. of vitamin K parenterally daily. The choice of anesthetic agents and premedication must be decided upon individually. Space does not permit adequate consideration of these choices here. Several recent publications are available which present this subject adequately.[9-11]

With diligent attention to early diagnosis, supportive therapy and prompt surgical correction we may look forward to the day when no loss of life results from intestinal obstruction in the newborn infant.

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EDITORIALS

Postgraduate Medicine FOR THE CONTINUING EDUCATION OF THE PRACTICING PHYSICIAN

Editor-in-chief: CHARLES W. MAYO, M.D.
Contributing Editor and Editorial Writer: MORRIS FISHBEIN, M.D.
Assistant Editor: SYLVIA COVET

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MEDICINE IN THE NATIONAL ECONOMY

Any evaluation of the economic status of a nation must take into account the health and longevity of its people. The people of the United States today have achieved an enviable position, as far as their health is concerned. Our life expectancy at birth for the population as a whole is exceedingly high. According to the latest reports of the Metropolitan Life Insurance Company, a white girl born in the United States can reasonably expect to live to 70.2 years and a white boy to 68.5. Our maternal death rate is now lower than that of any other large nation in the world and actually much lower than that of many smaller homogenous populations.

Since 1910 the five leading causes of death have changed from the order (1) tuberculosis, (2) pneumonia, (3) diseases of the heart, (4) accidents, and (5) diarrhea and enteritis to (1) diseases of the heart, (2) cancer, (3) accidents, (4) brain hemorrhage and (5) nephritis.

So complete has been the control of the infectious diseases that accidents now lead all other causes of death in persons from 1 to 24 years of age. The infant mortality rates have declined greatly. Our industrial workers have gained so greatly in health that 11½ years have been added to their life expectancy during the last four decades. As a result of rapid gains, the industrial worker is no longer at a disadvantage compared with other workers.

In the ultimate analysis the improvement in medical education from 1905 to the present is the basic factor responsible for all of our gains. Associated with this improvement in medical education has been the rapid expansion of public health services, including particularly the development of programs for the control of specific diseases, the expansion in the number of local health departments, the training of personnel and the delegation by the medical profession to health departments of certain phases of medical care.

In 1915 only 15 counties in the United States were served by local public health units under full-time health officers. By 1946, 1,322 counties had organized public health services. Many of the states have now recognized the importance of such public health units. A few years ago the American Medical Association gave full support to the delegation of federal funds for encouraging the development of full-time public health units. In December of 1950 its House of Delegates

revoked that approval and just now the legislative committee of the Association has restored its approval subject to certain minor modifications in proposed legislation. Recent legislative reports from Washington indicate the likelihood of enactment of this legislation in the near future.

HOSPITALS

The hospitals have assumed increasing importance in medical care since the turn of the century. We now have 6,572 hospitals which provide almost a million and a half beds with almost 17,000,000 admissions each year. On any given day at least 1,250,000 people are sick in hospitals in this country. The total births of the nation are about 3,500,000 per year and almost 3,000,000 of these children are born in hospitals.

The value of the hospitals and their equipment is estimated at $7,000,000,000. In the meantime the cost of conducting hospitals has grown so greatly that the cost per patient per day has risen from $3 or $4 in 1915 to $9 in 1945 and $14.33 in 1949. The patient pays only a portion of the cost. Four thousand of these hospitals are associated with Blue Cross plans of which there are now 85 functioning in 47 states. They paid the hospitals more than $300,000,000 in 1949. In addition to the hospital-approved plans, there are independent plans covering more than 66,000,000 people.

MEDICAL EDUCATION

Medical education costs the United States almost $70,000,000 a year. The increasing cost of medical education represented by equipment and personnel has forced students' fees to alarming heights, but even with the highest of students' fees the medical schools cannot maintain themselves.

Estimates as to the amount of money needed to keep the medical schools up to the standards required by the Council on Medical Education and Hospitals of the American Medical Association vary from $5,000,000 to $15,000,000 a year for the next 5 or 10 years. Toward this sum the American Medical Association has made a beginning and in the past few months has collected $600,000. It is now in process of attempting to increase this sum by an appeal to philanthropists and the medical profession; it seems doubtful that anything resembling the total amount needed can be secured by this technic. Personally I see no reason why federal funds could not be utilized for this purpose, particularly since the federal government regularly takes a larger and larger bite from the income of every person and business in this country.

It is sad that money suffers such terrible attrition in its travels from the home and community to Washington and back again, but until there is a change in our philosophy of government, it would seem that we must bear the penalty of the situation without permitting it to destroy our fundamental institutions. I have felt that those who receive federal funds should be able to protect themselves against federal domination—the situation requiring simply that those who receive the funds be as shrewd as those who dispense them. Unless we maintain the quality of medical education, we shall suffer the inevitable deterioration of all medical services.

The experience with accelerated curricula in World War II provided a bitter lesson for medical educators. They are not likely to consent to a return of an accelerated curriculum or to any system for half-educating prospective doctors under wartime stress.

The demand for doctors for the armed forces is, as might have been anticipated, just as furious and unthinking as it was in the recent past. Following World War II, great numbers of consulting bodies demanded that Army requirements of 6 doctors per 1000 men be reduced to 5 or 4 or even 3½. Now we are told that an Army of 3,500,000 men will require 7000 to 8000 additional doctors immediately, most of whom will come from the first category in recent classifications. Considering the physicians already in the armed forces, it would seem that the total proportionate numbers required have not been greatly reduced.

RESEARCH

The Steelman report to the President following World War II indicated that the nation now spends $110,000,000 annually on medical research, of which $55,000,000 comes from the government and the universities and medical institutes and the remaining $55,000,000 from industry. Mr. Steelman suggested that the needs of our times and the vast possibilities of benefit warrant an expenditure of at least $300,000,000 annually.

Much of our best research is carried on today through grants from the U. S. Public Health Service amounting to $70,000,000 per year, most of the funds going to private hospitals and private educational institutions. This represents a type of government cooperation with private agencies in which federal regulation and control is kept at a minimum.

Similarly vast funds raised by private philanthropies such as the American Cancer Society, the American Heart Association and the National Foundation for Infantile Paralysis stimulate research and bring results of value far beyond the funds that are spent. This represents the kind of cooperation between people and voluntary organizations and governmental establishments that only a democracy such as ours can sustain.

VETERANS ADMINISTRATION

In almost 40 years of intimate association with the problems of medical care in the United States, I have observed no other activity which has been subject to the abuses, the impositions, the actual fraud and the deterioration associated with the political domination that has been manifest in the Veterans Administration. I saw personally the disgrace of veteran care and the embezzlements and defalcation that marked the administration of Brig. Gen. Sawyer who was appointed by President Harding. I noticed at first hand the manipulation of veterans under the administration of General Hines.

With the end of World War II a renovating breath of decency accompanied the appointments of Gen. Omar Bradley and Maj. General Paul R. Hawley. Then came the enlistment of Dr. Paul Magnuson who became medical director succeeding General Hawley in 1948. From that moment the Veterans Administration began to benefit from the quality of medical education through the location of veterans' hospitals near medical schools and from the enlistment of leading teachers and clinicians in veteran care.

NEW LEGISLATION

The medical profession, made suspicious by repeated attempts of our present government to take over medicine in toto as a governmental function, has gone to the opposite extreme in advocating that government keep out of medicine entirely. One of these alternatives is just as impossible as the other. We must have mutual confidence, mutual respect, honesty and decency which are the only circumstances under which cooperation and coordination can proceed as they should to give the American people still further progress in the control of disease and the postponement of death.

MORRIS FISHBEIN

CURRENT COMMENT

AUTOTHERAPY

MANY years have passed since one L. D. Rogers of Chicago suggested for the treatment of all disease a system called autohemotherapy in which blood taken from the veins was allowed to stand in the open air for a while and then reinjected into the body. Somewhat later, an innovator named Duncan in New York worked out a technic whereby saliva was collected from ailing human beings and reinjected into their bodies. The theory behind this treatment was his observation that animals were accustomed to lick their own wounds as a part of the process of alleviation of suffering and healing.

Now comes a German investigator who says that in many dermatologic diseases such as

infantile eczema, urticaria and Quincke's edema, solar eczema, dermatitis venenata and even in cases of Raynaud's disease, he has seen striking results from auto-urotherapy. The urine is taken from the patient and injected under the skin, sometimes after previous sterilization by boiling. The dose varies from a few minims to five milliliters. As might be expected, the author claims also that the technic is useful in such conditions as migraine, asthma and the nausea and vomiting of pregnancy. The report is without the slightest control and the author says that he leaves the development of controlled evidence to larger clinics and laboratories.

In the United States investigators are still experimenting with a form of treatment which includes removal of blood which is subjected to irradiation with ultraviolet and then reinjected into the body. For this technic also remarkable results have been claimed in a number of conditions, many of which have now been quite positively determined as psychosomatic in character.

The distinction between scientific evidence and uncritical clinic impressions seems still difficult for many who report observations in medical publications.

MORRIS FISHBEIN

MARRIAGE AND MEDICINE

Among all the biostatistics that interest doctors those relating to marriage are not the least significant. Almost 1,675,000 marriages were recorded in the United States in 1950, or 5 per cent more than in 1949. Since the trouble with Korea came after the middle of the year and since the marriages during the first six months were below the 1949 record, the outbreak of what has been denied to be a war may have something to do with the excess for the last six months. Usually wars increase marriages, before the trouble begins and after it ends. The psychologic factors should be obvious, notwithstanding the warning of Mother Goose:

"Needles and pins, needles and pins,
When a man marries, his trouble begins."

The number of births in 1950 neared record proportions. Births were estimated at 3,700,000 with about 3,000,000 born in hospitals. During the last 10 years births have averaged 3,300,000.

Since both death rates and infant mortality rates have been steadily declining our population keeps growing. The excess of births over deaths annually is approximately 2,250,000.

In 1930 the maternal mortality rate in the United States was 4.4 per thousand live births; now it is near to 1. The improvement is credited to improvement in the quality of obstetrics, an increase in the number of specialists, more births in hospitals, the development of antibiotic drugs, the use and availability of blood transfusion, prenatal care and premarital examinations.

From the medical point of view marriage is wholly safe and desirable. From the social point of view experts recommend it. Still Sir John Davies said:

"Wedlock, indeed, hath oft compared been
To public feasts, where meet a public rout,
Where they that are without would fain go in,
And they that are within would fain go out."

Indeed, the books of quotations give marriage more quotes than almost any other subject. It has been called a "lottery," a "grave step," a "field of battle," a "lane where there is no turning," and a "community with a master, a mistress, and two slaves, making in all, two." The New Testament says, "It is better to marry than to burn," but Socrates when asked whether or not a man should marry replied, "Whichever you do you will repent it."

Be all this as it may, people have found more and more the value of the family doctor as a marriage counselor; marriage has aspects of health and wealth, of mind and matter, of character and the lack of it! The rush to marry in times of war is more determined by psychologic than by physical stimuli—a mutual seeking for someone sympathetic with whom to have a permanent bond. When the war is over, the seeking is for a home and rest and love and the immortality to be found only in the next generation.

MORRIS FISHBEIN

Men of Medicine

"Louse and Flea Farms"

When, last fall, Dr. Rolla E. Dyer was offered the newly created post of Director of Research, Emory University School of Medicine, he accepted the job with enthusiasm, the title with some reluctance.

"You can't *direct* research," he said. "Stimulate it, perhaps, but not direct. The man at the bench must always have a free mind and a free hand."

A veteran of 34 years with the United States Public Health Service—Assistant Surgeon General and Director of the National Institutes of Health from 1942 to his retirement in November 1950—Dr. Dyer remains staunchly devoted to the scientist at the bench and in the field. That devotion and respect are returned a hundredfold to the man who proved that murine (endemic) typhus in this country was transmitted from wild rat, by flea, to man, and whose reputation in the field of the rickettsial diseases is world-esteemed. At Emory, in Atlanta, Georgia, where he has been "stimulating" research since last November, his colleagues are eloquent.

"Dyer's not only a prime leader in the scientific thinking of the country, but he's a democratic, old shoe sort of guy," they say. "The more you know him, the more you like to work with him."

Dr. J. E. Scarborough, director of Emory's Robert Winship Memorial Clinic where Dr. Dyer has his office, says, "He's a great scientist and a medical liberal, but strictly a non-government man as far as private enterprise is concerned. Although everyone knows his major field is in the rickettsial diseases, he's also had a marked influence on the development of cancer research in recent years. While Dr. Dyer is officially in this department, you might call him a coordinator. Researchers throughout the building beat a path to his door."

The overstressed fiction that the pure scientist is all brain, no brawn, no warm blood and no humanity is happily disproved in Rolla Eugene Dyer. Lithe and wiry at 64, he looks 10 years younger and one would suspect his pure white hair and trim mustache were premature. A golf club or fishing rod would be as appropriate to his grip as test tube or scalpel, and he can chat as animatedly about a good book as about tularemia. He is a student of history and the classics and an alert and somewhat cynical interpreter of current events. He is a little proud of his distinctive first name, Rolla, which was his father's before him.

"My great-uncle *Rollin* was killed in a bushwhacker raid in Kansas during the Civil War," he explains. "Since he was the family hero, Dad was supposedly named after him—but the minister mumbled and the official records read 'Rolla.' Fortunately, I escaped being Junior and my family and friends all call me Gene."

Gene was born November 4, 1886, in Delaware County, Ohio, but was only a toddler when his father, an Episcopalian minister, was transferred to Bourbon County, Kentucky, where Gene and his older brother grew up in a rural community of some 3500 population. Neither incident nor accident shaped his later career and he was definitely *not* one of those precocious and rather obnoxious adolescents who poke at butterfly wings, cup up toads or hop breathlessly aboard the local G.P.'s buggy. On the surface, Gene displayed no scientific enterprise more original than the pragmatic conclusion that a borrowed bay gelding could get him to town faster and in greater style than shanks' mare. In school, and later at Kenyon College in his native Ohio, he was a whiz at history and the so-called dead languages which he taught for four years after receiving his A.B. degree *magna cum laude*.

Slowly, patiently, by trial and error and various humble efforts to finance his education—like a research scientist, in fact—Gene decided he'd like to be a doctor and, after graduate study at Cumberland University in Tennessee, he received his M.D. from the University of Texas, interning thereafter at Philadelphia General Hospital.

"That's where I met Esther Gibney," he says. "She was a graduate nurse and should have known better, but she married me the day I finished my internship and we borrowed $1000 and headed for Texas to be near my family. Took my state boards on our honeymoon in San Antonio and a job with a general practitioner in Marlin."

The job was straight horse-and-buggy-surgery-by-oil-lamp stuff and it lasted one month, or rather, young Dr. Dyer did. Gladly forsaking private practice forever, he sought and accepted a commission

as assistant surgeon in the U.S.P.H.S.

That was in 1916. That was the beginning of a relationship with the rat, the tick, the flea and the guinea pig that was to prove lasting and intimate—so intimate, indeed, that Dr. Dyer has voluntarily and involuntarily shared his life's blood with his arthropod associates! The tiny arthropod—"varmint with skeleton on the outside of his body" is the doctor's definition—remains one of man's most formidable foes as the known bearer of typhus, spotted fever and other debilitating, often fatal, diseases. Among the great scientists who have proved the transmission of disease by these "varmints" is Rolla E. Dyer. His researches into the origin and spread of murine typhus led indirectly to the development of vaccine with which all troops were inoculated in World War II, with the result that not one American soldier died of typhus.

But lifesaving and history-making discoveries did not come overnight to the young searcher, nor were the fellowships and awards he now carries lightly earned. Early in his public health career he was engaged in control of bubonic plague in Louisiana and Texas; research on pellagra under the invaluable direction of Dr. Joseph Goldberger in South Carolina; sanitation work at Camp Merritt, New Jersey in World War I, followed by field study of the influenza outbreak, 10 hot months as epidemiologic aid in Little Rock, Arkansas, and four months in a similar post in Trenton, New Jersey. The latter job ended abruptly in 1921 when funds ran out.

"What would you really like to do now?" Dr. McLaughlin, head of the Division's Communicable Disease Control, asked Gene.

"Take a course at the Hygienic Laboratory in Washington," young Dr. Dyer answered promptly. Wasn't the Hygienic Laboratory, a unit of the P.H.S. Division of Scientific Research, the chief training center for smart young officers interested in scientific technics? Hadn't the war, so recently over, increased the Laboratory's field activities to cover the major public health problems of nation, state and community?

The Hygienic Laboratory which, in 1930, became the National Institutes of Health, accepted Gene's wide-eyed arrival with something less than enthusiasm.

"Don't know what to do with you," Dr. George McCoy, the Director, mumbled, and passed the newcomer along to his assistants who mumbled the same thing. Somewhat deflated, but not licked, Dr. Dyer was first man at the bench the following morning, hard at work making an agar culture when his colleagues drifted in. Within a year he was assistant director of the Laboratory and his chief, Dr. McCoy, was giving him every possible encouragement and opportunity—including a year of foreign study in 1923-24, financed by the League of Nations.

In the great research institutes of Paris, London, Copenhagen and Hamburg Dr. Dyer furthered his studies—especially those in tropical diseases. Many times since he has gone back to those institutes, and journeyed to still farther outposts, and been honored by the scientists who once taught him. But while he remains forever impressed by European knowledge of basic sciences, he makes no apology for American achievement, and says the best part of foreign travel is the first glimpse of home. Perhaps his pretty, vivacious and intelligent wife, Esther, and three children—a son and two daughters—had something to do with that joy of return, plus the frequent calls for epidemiologic help from our own cities and rural areas.

Prior to his intensive research into the nature of the rickettsial diseases in the thirties, Dr. Dyer did special work on scarlet fever antitoxin and, with the assistance of B. T. Sockrider, published a still authoritative paper, "Results obtained with the Dick test before and after immunization with the toxin of the hemolytic streptococcus of scarlet fever."

Then, in the late summer and early fall of 1929, Drs. Dyer, A. Rumreich and L. F. Badger were assigned by the P.H.S. to investigate the method of transmission of typhus. An emulsion from about three dozen fleas, obtained from rats which had been trapped on premises near food-handling establishments in Baltimore, was injected into guinea pigs which contracted a disease similar to typhus. Their clinical symptoms and the appearance of their organs and tissues resembled those of pigs which had previously been inoculated with a strain of American or New World typhus (sometimes called Brill's disease) which is milder in form than the louse-borne typhus. Dr. K. F. Maxcy, also of the Public Health Service, had done prior research on the endemic, American form of typhus, comparing it with the more virulent, epidemic European form, and had obtained no evidence that it was louse-borne, as is its more vicious sister. Dr. Maxcy had also pointed out that individuals employed in food-handling establishments were more prone to the disease than the general population and that a reservoir possibly existed in rats. Thus Dr. Dyer progressed from the theory that a rat reservoir must exist—and was successful in isolating the virus (from fleas found on rats) which causes endemic typhus, proving its transmission from rat, by flea, to man.

On July 13, 1931, Dr. Dyer, aided by Dr. Rumreich and Dr. Badger, published their conclusions: "It would appear definitely established that the disease typhus has two manifestations known at present," he wrote; "the first and better known, a louse-borne disease of great communicability

"... A free mind and a free hand."

from person to person, in times of overcrowding of unclean population and characterized by its tendency to the formation of epidemics; the second, a disease primarily of rodents which is apparently transmitted from rat to man by rat fleas. This manifestation of typhus seemingly is not transmitted from man to man and is therefore characterized by the tendency to remain endemic."

In the course of his investigation of typhus, Dr. Dyer acquired the disease—but dismisses that fact lightly, disputing his wife's dimmer view of his serious illness. During his more than 30 years with the P.H.S. he has seen some 200 cases of laboratory infections with various diseases, despite the utmost caution, and at least five deaths. The Memorial Laboratory, ninth and most recent addition to the National Institutes of Health in Bethesda, Maryland, is dedicated to those heroic men and women of the U.S.P.H.S. who gave their lives in the cause of research. Fortunately, Dr. Dyer is still sprightly, although a lesser man might have succumbed to his hazards and actual illnesses in the line of duty. As a researcher he often invited trouble.

Dr. R. C. Williams, a colleague of many years, whose history of the United States Public Health Service will soon be published, recalls the days in Washington when Gene was playing dangerous games with his typhus fleas, and also with lice.

"One of those fleas is going to get loose and bite you," he warned ominously.

"Not *me*!" Dr. Dyer said smugly. "I've taken care of that. Jimmy, my pet rat, has the run of the lab and any stray fleas will settle on him."

On a subsequent visit to the laboratory, Dr. Williams had confirmation. Jimmy, unrestrained, ran half way up his pant leg! Some time later the Dyers were entertained by the Williams at dinner and Gene complained bitterly about his poor fleas and lice which were having difficulty that winter in propagating themselves. Occasionally, during the course of a convivial evening, he reached down and scratched his leg.

"Flea bite you?" Dr. Williams inquired causically. "Not fleas this time—lice!" Proudly, Gene rolled up his trouser to reveal a small box, strapped to a shaved area on his leg. He'd brought a select company of his undernourished lice along for dinner! That was a voluntary giving of his blood to science. *Involuntarily,* he became the first recognized case of human Q fever in the United States.

Q FEVER is caused by a rickettsia—one of those gram-negative micro-organisms found typically in arthropods. In 1935, Drs. Frank M. Burnet and E. H. Derrick began investigations in Australia on a new disease they dubbed Q fever because they questioned what it was. This disease was found among slaughter-house workers in Queensland and was caused by a rickettsia, named *Rickettsia burneti,* that was also found in ticks whose favorite host was the bandicoot, a small native mammal. Simultaneously, in the U.S.P.H.S. Rocky Mountain Laboratory, Hamilton, Montana, Drs. Gordon Davis and Herald Cox isolated a rickettsia-like infectious agent from ticks found along Nine Mile Creek, named the disease Nine Mile Fever and the rickettsia, *R. diaporica.* Neither the Australian nor the Montana scientists were aware of each other's experiments until Dr. Dyer provided the missing and connecting link—the hard way!

In 1938 the then Chief of the Institutes' Division of Infectious Diseases spent four days in the Montana laboratory, handled some guinea pigs that were carrying *R. diaporica* and, about a week after his return to Washington, literally became as sick as a dog.

The eternal scientist, Dr. Dyer quit shaking and sweating long enough to direct that a guinea pig be inoculated with his blood. Identification of *R. diaporica* followed, proving that Dr. Dyer was the first human known to have contracted Nine Mile Fever. Stimulated by this discovery, he decided to experiment further with the organism isolated from his remarkable blood, testing it against the micro-organisms of Australian Q fever that had been sent in mouse spleens from Dr. Burnet's laboratory. Not only was his blood positive, but five recovered guinea pigs, previously inoculated with the Q strain, proved to be immune to the Dyer strains! More infected mouse spleens were sent from Queensland, more checks and counter-checks were made, all showing that the abattoir disease of Australia and the Montana Nine Mile Fever were closely enough related to be called henceforth one and the same—Q fever!

There is no purple heart in the Public Health Service, but there are steady opportunities for advancement and, best of all, for its vigilant, tireless officers, the never-ending challenges of nature and history. A student of history as well as of science, Rolla E. Dyer was a fine man to have at the helm of the nation's medical research during World War II. In 1942 he became Director of the National Institutes of Health and thus Assistant Surgeon General, P.H S. Although he left the laboratory bench to become an able administrator, he was never far from it.

Since 1939 activities of the Institutes had been emphasizing war research—problems directly related to mobilization. Among other things, typhus vaccine had been developed by Herald Cox in Montana; stockpiles of quinine were built up for the civilian population at the same time new therapeutic agents for malaria were sought and developed; plans for collecting blood and safely standardizing its processing for plasma were work-

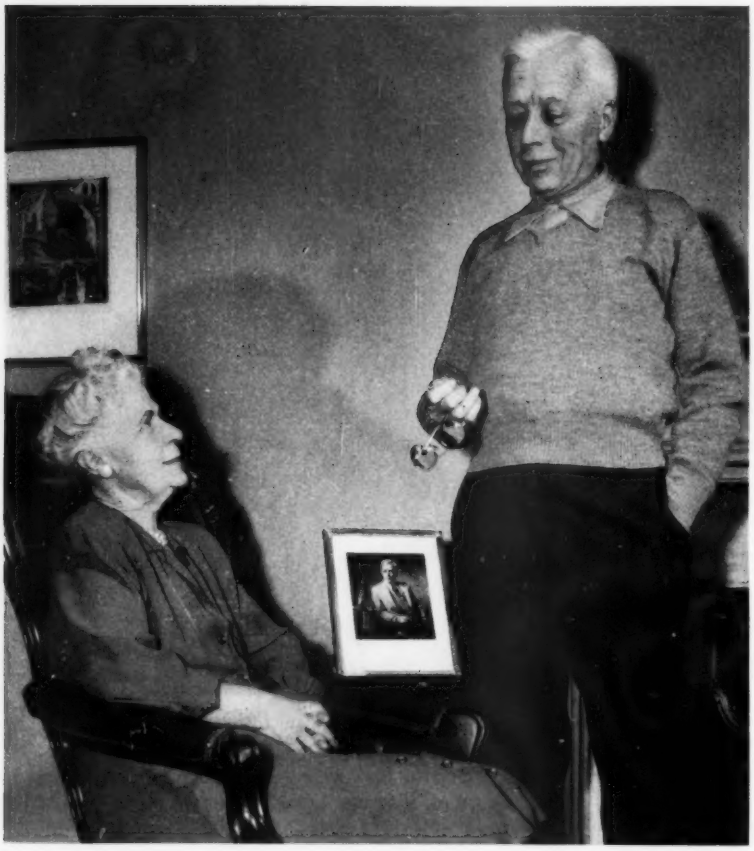
An old hand at the bench, Dr. Dyer glances up from the microscope.

ed out. Before and during the war years Public Health researchers conducted intensive studies in the hazards of new substances in war industries as well as vital research into tropical medicine. And all the time the basic researchers went on to improve and safeguard the health of a world that might one day be at peace.

Until 1945, Dr. Dyer's tasks as director of this vital research were manifold and staggering. There was little time for his family nor for the hobbies he'd nurtured through the years—reading, refinishing old furniture, raising vegetables in his garden, surf casting off the Florida gulf coast, tinkering with the clocks he'd been collecting around the world. When he wasn't traveling at least he could live with the lovely things that he and Esther had acquired and slaved over, the antique tables, chests of drawers and love seats that had been sanded and rubbed down to the original and exquisite grain. He could be thankful for a lively, still pretty and cooperative wife, as busy with her wartime chores as he with his, and children—grown now—who forgot urgent personal demands in a greater emergency.

With the coming of peace came still greater expansion of the Institutes, which had been authorized by Congress in 1946 to buy adjoining land in Bethesda, thus increasing the 91 acres to 311. Congress, Dr. Dyer says with gratitude, has always been extremely interested in medical research and more than willing to cooperate. In 1945, when the Office of Scientific Research and Development terminated its cooperative programs in medical research—programs that had amounted to some $7,000,000—he was instrumental in getting funds from Congress for the N.I.H. to take over some 250 uncompleted contracts for research that would otherwise have been choked for lack of funds. For this endeavor, and other achievements, Dr. Dyer received the Lasker Award in 1948, one he values highly among his collection of certificates and medals which includes: Carlos J. Finlay medal, Cuba, 1944; Office of the Order of Public Health of France; U. S. Typhus Commission Medal, 1944; Sedgewick Memorial Medal, A.P.H.A., 1950 and the Walter Reed Medal, American Society of Tropical Medicine, 1950. His fraternities, fellowships and honorary lectureships are legion and a little unbelievable to this modest man who, incidentally, still dreads making a public speech.

His audiences do not share his suffering. He speaks clearly in the precise, guarded idiom of the scientist when describing his research, but brightens his less technical subjects with the flair and



Dr. and Mrs. Dyer in their attractive home, a few blocks from the hospital. The portrait on the table between them is a copy of the original painting which now hangs in the National Institutes of Health, along with those of other past directors of the Institutes.

(Photos by Morgan Fitz)

vocabulary of the erstwhile teacher. The James D. Bruce Memorial lecture on preventive medicine is his most recent one, delivered before the American College of Physicians at St. Louis on April ninth of this year. Dr. Dyer's timely paper, "Preventive Immunization in a National Emergency," will be published in the *Annals of Internal Medicine*. At this writing, funds are being banked in Bethesda for the establishment of a Dyer Lectureship to provide the honorarium for an annual speaker from some worthy research institution.

In addition to the title of Director of Research, at which he carps, Dr. Dyer is, or soon will be, listed as Professor of Medicine at Emory. He lives within a mile of this University's beautiful campus, in a new and charming three-bedroom brick house, furnished with the collectors' pieces (and clocks) made functional and valuable by their owners' elbow grease and skills. There is nothing antique about the kitchen or utility room, however, equipped with every electric device known to culinary or housewifely science! Surely an old laboratory hand will be found tinkering there, freezing his home-grown vegetables, or watching the centrifuge in the shiny chrome washer—as much as the classicist and historian will relax in the needlepoint upholstered rocker (Esther's needlepoint, of course) flanked by his book shelves and enthralled by a Beethoven symphony.

Both Dr. and Mrs. Dyer hope that there will be time for leisure pastimes now, certainly more time to enjoy the children and grandchildren who, by happy accident, are all located within a few hundred miles of Atlanta. But leisure after work, of course. Retirement from the U.S.P.H.S. is mandatory at 64, but here at Emory is a new job to tackle, perhaps the most stimulating of all. Here there are young men beginning their scientific explorations into the unknown to counsel; older men with important discovery at their fingertips, and long-time Public Health cronies nearby who still doggedly track and trace the carriers of disease. A wise but eager explorer himself, Gene Dyer will never rest overlong in that needlepoint rocker.

JEAN DEWITT FITZ